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PHYSIOLOGICAL REVIEWS

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PHYSIOLOGICAL REVIEWS

VOL. 27 APRIL, 1947 No. 2

ON THE NATURE OF PAIN

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Concepts Concerning Pain. Views about the nature of pain have varied, but from Aristotle to relatively recent times there has been general agreement on one major issue, namely, that pain is a "passion of the soul", a feeling state, or a "quale", and not a specific sensation. Such a view was supported by thoughtful workers in nineteenth century Germany, England and America (1).

As recently as the turn of the twentieth century it was still considered debatable whether pain is indeed a sensation or exclusively a feeling reaction akin, but opposite, to that of pleasure. The following is representative of the prevailing view of that period: ". . . that pain is not a sensation but a form of feeling; that it is not to be classed with the sensations of touch, or temperature, or heat; that it does not have peripheral end organs, and that there are no nerves in existence which, on irritation alone, produce pain; that there is no such thing as a pain tract. . . ." (2).

However, there has been a gradual change in this conception and the basis for modifying this earlier view is briefly summarized in the following paragraphs.

1. Blix (3), Goldscheider (4) and von Frey (5) noted that when the skin is explored with stiff hairs, pain alone may be elicited from certain areas. The structures stimulated have been indentified by Woollard, Weddell and Harpmann (6) who demonstrated that cutaneous pain is subserved by the finer medullated and non-medullated nerve fibres bearing free endings. These fibres and endings are specific and are arranged in a plexiform interlocking manner. Weddell (7, 8) in order to determine the neurohistology of skin from which pain alone could be evoked, outlined the pattern of sensory loss in a patient with a sciatic nerve lesion. The area from which pain could not be aroused was smaller than that from which touch could not be aroused, and this in turn was smaller than the areas over which temperature sensibility had been lost. A piece of skin 2 by 3 cm. was stained and removed from a zone in part of which pain only could be aroused and in part of which pain and touch could be evoked. In the area from which pain alone could be elicited, fine nerve fibres were seen giving rise to superficial nerve nets; no thick nerve fibres or organized endings were seen. On the other hand, in the area of skin in which both pain and touch could be evoked, the cutaneous nerve plexus was seen, together with thick nerve fibres ending around hairs and thinner fibres giving rise to superficial nerve nets.

Tower (9) introduced the useful concept of the "sensory unit" as contrasted with the single afferent nerve ending. She has made it seem likely that a "sensory unit" consists of many nerve endings, all branches of a single fibre,

connected with a single cell in the dorsal root ganglion. An area of skin (12) or cornea (9) of about a centimeter in diameter is said to be supplied by such a single unit and it is conceivable that larger units exist. Many pain fibres supply overlapping "sensory units" to a given area, although there is no connection between the endings of different fibre units. It would thus seem likely that the painful spot experienced as such when an area of normal skin is exposed to noxious stimulation is a centrally integrated experience projected onto the periphery for the specific purpose of localization. The "skin spot" is, so to speak, a "mind spot".

2. An answer to the question as to whether pain is a specific sensation or whether it results from overstimulation of fibres serving other sensations, such as touch or warmth, is the demonstration in patients (10), that pain alone and no other sensation may be lost in limited regions of the body as a result of accidental injury of the spinal cord. Also, after surgical transection of the spinothalamic pathways, pain alone may be absent in circumscribed regions without associated loss of temperature or touch (11).

Moreover, it has been demonstrated by Adrian, Cattell and Hoagland (12) and by Cattell and Hoagland (13) that intensive stimulation of tactile end organs up to the capacity of the corresponding nerve fibres to conduct does not elicit evidences of pain.

3. Further indication that pain is a specific sensory experience with its own neural structures and properties has been afforded by the analysis of the action of certain analgesic drugs. These agents were capable of specifically raising the threshold of pain from 35 to 80 per cent above the control level while they lowered or left unaltered the threshold for the perception of touch, hearing, smell, two point discrimination and the perception of vibration. It has been observed that acetylsalicylic acid actually lowers the threshold for warmth (14, 15, 16, 17).

4. There is evidence to indicate that certain structures are equipped for and give rise to the sensation of pain only. The teeth, the middle meningeal artery and the arteries at the base of the brain and at least some of the scalp arteries, such as the temporal artery, seem to be equipped with afferent fibres which, as far as consciousness is concerned, conduct only those impulses which result in pain (18). However, at least one other sensation, i.e., cold, and possibly touch as well as pain can be elicited by suitable stimulation of the cornea (19).

On the other hand, there are certain areas in the body from which pain cannot be elicited, for example, the parenchyma of the brain (18). Also, such an area is found on the inside of the cheek opposite the second lower molar (20). In short, it is necessary to infer from the evidence that the pain experience is first a sensation derived from noxious impulses traversing specific pathways. Such phenomena may be followed by the familiar and predictable feeling states and other reactions.

Neural Structures Involved in the Conduction of Noxious Impulses Giving Rise to Pain. All fibres carrying noxious impulses experienced as pain enter the spinal cord or brain stem through the dorsal root ganglia. The superficial

pain impulses are usually conveyed by the somatic nerves and enter the cord more or less directly through the dorsal roots. Deep pain impulses may approach the central nervous system in a number of ways: some are conveyed by pain fibres which attach themselves to blood vessels part of the way and then join autonomic nerves; other deep pain fibres from their very beginnings are closely associated with autonomic nerves and remain so affiliated until relatively near the cord; and still other deep pain fibres join with somatic nerves. The course they assume in approaching the dorsal root ganglia is irrelevant to a consideration of the quality of pain or the reflexes aroused (21, 22, 23, 24, 25, 26, 27, 28).

Although pain endings are usually naked and umyelinated, with or without slightly swollen twigs, there is no uniformity about the size of fibres which conduct noxious impulses to the cord and brain. Fibres conducting pain impulses may be roughly grouped as regards speed of conduction of impulses into slow and rapid, involving respectively small and large calibre fibres (29, 30). It has been shown by Gasser (30) that the gamut of size involved in the conduction of noxious impulses giving rise to pain is wide, spreading from the very smallest to large calibre fibres.

After entering the cord all noxious impulses are conveyed across to the opposite side where their pathways are localized in the anterolateral portion of the spinal cord. The fibres of the spinothalamic tract pass into the nucleus centralis posterior of the thalamus. They do not terminate in any of the adjacent nuclei nor go into the anterior portion of the thalamus. The cortical projection from the nucleus centralis posterior is predominantly to the post-central convolution. There is in this projection a definite topical organization so that those fibres from the medial portion of the nucleus (cephalad parts of the body) end in the lower part of the gyrus; those from the lateral portion (caudad parts of the body) in the paracentral region; and those from the middle, in the intermediate region.

It is probable that the brain structures involved in pain perception occur in both cerebral hemispheres in the region of the central fissure (31, 31a, 32). Complete hemianalgesia is rare after destruction of fibres in either hemisphere. More specifically, pain from the face seems to have both homolateral and contralateral cortical representation so that unilateral hemispherectomy does not result in analgesia of the face. Although the thalamus is important in the integration of neural activity having to do with pain, the cortex is essential to discriminations involving localization and intensity. Excision of a small portion of the left post-central cortex has resulted in elimination of phantom limb pain for a period exceeding 4 years (32a). That there is also mid-brain sensory integration is suggested by the survival of pain sensation after destruction of the fibres entering the thalamus and cortex.

Qualities of Pain and Their Significance. For purpose of gross classification superficial and deep pain are recognized. Pain resulting from noxious impulses originating on the surface or superficially has a pricking, bright, burning, itching quality, and is highly localizable. It commonly incites action such as fight or flight. Pain resulting from deep noxious impulses is a deeper, diffuse pain,

has an aching quality and localization is less precise. It often induces nausea, sometimes fall in blood pressure, prostration and syncope and usually causes the animal to seek protection in withdrawal, inactivity and rest. There are minor differences in the deep pain from muscle, web and artery. Structures of endodermal origin are said to be relatively poorly supplied with pain fibres as compared with those of mesodermal or ectodermal origin (26).

Man's ability to experience pain is not essential to a suitable biological adjustment. Persons congenitally without the ability to experience pain adequately adjust themselves to their environment, as do persons who have had pain pathways surgically interrupted (33, 34). Alarm or defense reactions may be initiated by any stimulus if that stimulus has been previously associated with injuries, dangerous threat situations or frustrations. As a matter of fact, the bulk of such reactions involved in common experience are initiated by non-painful stimuli. Pain is an accessory though important and final warning of the imminence of tissue damage.

On the other hand, persons critically ill, as with terminal neoplastic disease, and those gravely injured do not inevitably experience intense pain. Indeed, the intensity of pain is not directly proportional to the extent or seriousness of tissue damage. In a combat zone during World War II Beecher (35) questioned 215 recently wounded men concerning the intensity of the pain they were experiencing. These men had sustained extensive soft tissue injuries, compound fractures or penetrating wounds of the head, chest or abdomen, but were mentally clear. Only twenty-four per cent had "bad pain" whereas the remainder had moderate, slight or no pain.

Pain Threshold. Pain is best investigated in conscious man, otherwise its study resolves itself into an analysis of reactions. Hence, at the outset a fundamental distinction must be made, namely, between the perception of pain and its associated reactions. A starting point for a quantitative analysis of pain perception can be made by defining the pain threshold and by ascertaining its properties, and how it can be modified (36, 37).

The pain threshold sensation may be defined as the lowest perceptible intensity of pain. The pain threshold stimulus is that amount of stimulus required to induce threshold pain and may for convenience be expressed in standard physical terms. In accordance with common usage the pain threshold is considered to be raised when more stimulus is required to induce threshold pain; conversely, when less stimulus is required the pain threshold is said to be lowered. Pain is unique in that many methods of stimulation can evoke it. Both superficial and deep pain can be elicited by thermal, electrical, mechanical and chemical stimuli. It is only necessary to choose a stimulus, the strength of which can be controlled and measured, which will allow a clearly definable end point of perception, and one which will not of itself introduce excessive variability into the observation.

For the establishment of the threshold of pain the verbal report of an instructed subject is the most reliable evidence. A verbal report of an end-point has been successfully used in the researches on other sensations and in

studies on cutaneous pain has yielded reproducible data. Muscle twitch, blinking, withdrawal or any similar response indicating reaction to pain should be noted together with, but independently of, the verbal report of the pain threshold of a human being.

1. *Methods.* Ivy and his colleagues have considered all the methods that have been used for measuring the pain threshold and have listed a complete bibliography (38). Many methods for ascertaining the pain threshold have produced data which have been difficult of interpretation. This is possibly because of a) the failure to establish a known relationship between the quantity measured as the stimulus and the amount of pain producing disturbance in the environment of the pain endings; and b) the fact that reaction to a noxious stimulus is often confused with perception of threshold pain.

For example, in electrical stimulation of the teeth the amperage, voltage, frequency and resistance in the circuit are all of importance in inducing pain. Measurement of one of these quantities as the pain threshold might be expected to lead, because of its indirect relationship to the amount of disturbance in the environment of the pain endings, to considerable variability. Indeed, this has been found to be the case for this method of investigating pain threshold by Ivy et al, by Roth and Kleitman and by Robertson, Goodell and Wolff (38, 39, 40, 41). These same general criticisms also hold for the mechanical methods for eliciting pain, such as measuring the pressure required to evoke pain in the esophagus, the gut, or in the skin (42).

Chapman and Jones (42) measured the pressure required to induce pain in the esophagus by distention, and Harrison and Bigelow (43) also studying deep pain measured the point at which pain occurred in working ischemic muscles of the forearm.

Other investigators, notably Libman (44) and later Hollander (45) whose investigations were directed toward estimation of the threshold for pain perception actually tested reactivity. Libman exerted pressure with his thumb upon the styloid processes of human subjects and found that prize fighters, Negroes and American Indians as groups failed to react to such noxious stimulation of intensity great enough to induce a reaction of discomfort in the average white city dweller.

Hollander's instrument was a rough, metal grater incorporated in a sphygmomanometer cuff. He inflated the cuff and noted the pressure at which the subject winced. He, as did Libman, reported that relatively stoical people have a high threshold for reacting to noxious stimulation.

In spite of the above mentioned quantitative and conceptual inadequacies of many methods for studying pain threshold they have contributed much to the general body of information concerning the pain experience. Any serious consideration of the nature of pain sensation must take full account of the data derived by these methods.

Bazett and his colleagues have demonstrated that all sensation elicited by heating the surface of the skin is the direct result of the change in the thermal gradients near the skin surface (46). Also, it has been demonstrated that the

change in the thermal gradients in the skin is directly proportional to the intensity of the thermal energy brought to bear upon the skin (47), thereby demonstrating that this quantity, measured as the stimulus, is directly proportional to the algesic, that is, the amount of pain producing disturbance at the pain ending. This stimulus can be expressed quantitatively in gram calories/second/cm.^{2} Therefore, to measure the threshold of cutaneous pain the thermal irradiation of the skin has proved to be satisfactory and by this method both pricking and a burning pain threshold can be ascertained (37, 48). For most experimental purposes, a pricking pain threshold is more convenient. Most of the observations on cutaneous pain considered below are in terms of pricking pain threshold.

2. *Uniformity of the Cutaneous Pain Threshold in Man.* It was observed that successive observations of the pricking pain threshold on the forehead of a single individual could be reproduced within ± 3 per cent (thermal irradiation method). The pain thresholds for a group of 200 individuals were thus measured (49). They were found to require the same intensity of stimulus to evoke pain, that is, 0.218 gram calories/second/cm.^{2} with a standard deviation of ± 5 per cent, maximum variation of ± 15 per cent. The group of 200 included individuals of both sexes from ten to eighty years of age.

In order to ascertain whether pain threshold varies with the emotional states of the subjects, measurements were made in three individuals at the same time each day over a period of several months. Immediately preceding the measurement each day, the subjects recorded a statement of their estimated general effectiveness and mood. Although during this period these estimates showed wide variation, the pain threshold measured in these subjects did not vary beyond normal limits nor consistently with the general effectiveness or the emotional state. Also, throughout a twenty-four hour period of enforced wakefulness the pain thresholds were uniform and normal (49).

From these data it is inferred that the pain threshold in man is relatively stable and uniform when measured in the manner described. Furthermore, it is independent of age, sex, various emotional states and fatigue, and the time of day within the limits of the ability of the subject to maintain proper attention (37, 49).

Factors Which Influence Measurement of Cutaneous Pain Threshold in Man. Having established the conditions for the uniformity of the pain threshold, the factors that alter it may be considered. These may be roughly classified as physical, physiological, chemical and psychological.

The several physical factors which were observed to affect the pain threshold are those that vary the rate of heat loss from the skin. Also, the thickness of the skin (calluses) and the skin temperature, alter the amount of energy required to elicit pain. Variations in the intensity of stimulus required to elicit threshold pain on different parts of the same body may be accounted for by these factors. To eliminate these physical factors most tests were made on the forehead because the skin temperature of the forehead and the thickness of its skin are uniform from person to person. Starting with the periphery

it is evident that two effects may be expected from the peripheral endings responsible for pain. The threshold may be lowered by traumatic deformation, denudement or injury of tissues near these endings. There is experimental evidence that the pain threshold may be lowered as much as fifty per cent in sunburned skin (50). Other experiments show that by local anesthetization the threshold can be greatly raised or even obliterated. Obviously, blocking or cutting through a nerve fibre prevents it from carrying any impulses.

When a peripheral nerve is slightly injured, as by sustained pressure, a pin prick administered with constant force may feel less sharp, although the pricking pain threshold in the area of skin supplied by that nerve may be normal. However, if the nerve injury be sufficiently great, not only do pin pricks feel less sharp, but the pricking pain threshold, as ascertained by the radiation technique, is raised.

A raised pain threshold was observed in hypoalgesic areas of skin in patients with syringomyelia and damage of the spinothalamic tracts. A stimulus strong enough to cause blistering was sometimes required to evoke pain. In patients with lesions in the region of the internal capsule, elevated pain thresholds were also observed in the involved areas of skin, where pin prick felt less sharp. Furthermore, in patients with so-called central pain and lesions near the thalamus, with burning sensation and other paresthesias associated with the complaint that pin prick felt sharper than normal, the pain threshold in the involved painful area was usually elevated and never depressed (37, 48).

Also, there are other factors that may change the level of the pain threshold (37). Distraction, suggestion and hypnosis have been demonstrated to raise the pain threshold as much as thirty-five per cent. It is also observed that certain persons, during periods of fatigue, lethargy, suggestibility, prejudice or anxiety were unable to focus on the procedure or to maintain an objective attitude toward the sensation. In such persons the pain threshold varied greatly and was unpredictable. In the assay of analgesic agents, the attitudes and attention of the subject became especially important. Entirely different measurements of pain threshold were obtained depending on the ability of the subject to give attention to the assay. In a suggestible or prejudiced subject placebos significantly raised the pain threshold, whereas ordinarily effective amounts of analgesics produced minimal pain threshold raising effect (51).

It has long been known that "of two pains occurring together, not in the same part of the body, the stronger weakens the other" (Hippocrates). A corollary of this ancient observation is the experimental demonstration of a raised pain threshold in persons experiencing pain spontaneously or with pain experimentally induced. Gammon and Starr (52), although they were concerned with the effects on intensity of sustained pain rather than on pain threshold made similar observations. According to these authors the intensity of sustained deep pain induced by the subcutaneous injection of ten per cent sodium chloride into the arm is appreciably, though temporarily, reduced by stimulation of the skin adjacent to the area of pain. The intensity of pain was modified not only immediately after the application of the counter-irritant, but again

immediately after it had been withdrawn. In pain due to ointments applied on the skin, only cold applied to the painful areas reduced its intensity.

Effects of Analgesics on Pain Perception. Predictable effects as regards elevation of pain threshold were obtained with a variety of analgesic agents (14, 15, 17, 53, 54, 55, 56, 57, 58, 59). Also, maximal analgesic effects were achieved by given amounts of a drug and larger amounts within pharmacological limits produced no further threshold raising effect (14, 15, 59). However, as one approached narcosis following very large amounts of an analgesic agent, further threshold elevation was achieved (59). With smaller amounts, the effect on the pain threshold was proportional to the amount. Each of the drugs studied had its own maximal or ceiling amount which produced the maximal threshold raising effect. Furthermore, analgesics acted on pain with approximately the same effectiveness whether the noxious stimuli were conducted by smaller or by larger fibres (48, 59).

To ascertain whether these generalizations concerning threshold-raising effects are valid for deep pain as well as for cutaneous pain, Harrison and Bigelow (43) used a modification of Lewis' method for inducing deep pain (26). By repeatedly clenching the fist at the rate of once per second, after establishing asphyxial block by means of a ligature about the upper arm, a predictable number of contractions could be established as the threshold for pain. It was observed that the number of contractions of the hand necessary to induce pain was increased after analgesics. In terms of percentage, the effect approximated that for the cutaneous pain threshold obtained by the radiation technique. Thus, the aforementioned generalizations concerning the action of analgesics are valid for both cutaneous and deep pain. Moreover, there exists no satisfactory evidence to support the view that one or another analgesic agent is dependent for its effects upon the type or the source of pain.

Experiments were performed to ascertain whether there be a quantitative relationship between the change in pain threshold resulting from the action of an analgesic and the intensity of pain produced by standard stimuli well above the threshold (60) (see next section). It was observed that after the administration of a threshold-raising agent, the estimation of experimentally induced pain is strikingly modified. Thus, when the pain threshold is raised approximately forty per cent, stimuli which previously induced pain of three plus intensity are no longer painful, and those stimuli that normally induce pain of seven to eight plus intensity induce pain of three to four plus intensity.

Quantitative study of the effect of an analgesic agent in reducing the intensity of the spontaneous pain of disease is just beginning. This important question has not been approached hitherto because of lack of experimental methods, and because deductions regarding analgesic action have been made largely from the agent's effects upon the pain threshold of normal subjects. Some of the difficulties of interpreting these data in terms of the individual in pain have been pointed out above.

It has long been known that pain is a powerful antagonist of morphine action, and it has been demonstrated that prolonged pain diminishes or obliterates

the threshold-raising action of morphine (14). Depending on the time the painful experience was experimentally introduced in terms of the curve of threshold-raising effect of the morphine, a greater or lesser degree of disturbance in threshold-raising action was observed. Thus, if a pain of a given intensity and duration was experienced in the course of the action of an analgesic agent, it modified the threshold-raising effect but little. If it was experienced early in the course, a gross reduction of threshold-raising effect was observed. Despite the fact that there was relatively little elevation of pain threshold under the latter circumstances, the subjects seemed to be indifferent to the occurrence of pain. Although pain may be recognized as such, the individual seems to lose his anxiety and other reactions that usually accompany pain perception. It would appear, then, that with morphine one can demonstrate the distinction between pain perception and pain reaction.

The Discrimination of Intensity of Pain. A new approach to the study of the pain experience has been made in attempts to evaluate the intensity of pain above the pain threshold and to correlate this evaluation with the intensity of the evoking stimulus. Experiments of this nature on other sensations, particularly vision, hearing and heat, have been carried out and have added much to the understanding of the sensory mechanism involved (60, 61, 62, 63, 64, 65).

The ability to discriminate small differences in intensity of painful stimuli has been investigated by means of the thermal radiation method (60). This discrimination was studied in the intensity range from the pain threshold (218 millicalories/sec./cm.^{2}) to intensities of more than twice this value (480 millicalories/sec./cm.^{2}). It was found that from the pain threshold to forty-five per cent above, it was possible to distinguish differences in intensity of painful stimuli of ± 4 per cent of the threshold stimulus. As the intensity of painful stimulus was increased beyond 345 millicalories/sec./cm.^{2} this keen discrimination gradually diminished. With intensities of 480 millicalories/sec./cm.^{2}, i.e., more than twice that of the pain threshold, differentiation for higher intensities was no longer possible. Between threshold stimulus and the stimulus beyond which no further discrimination was possible (i.e., the highest intensity of pain which can be perceived), approximately twenty-one just noticeable differences of pain intensity could be distinguished. With the higher intensities of stimulus tissue damage occurred.

In this connection it is important to point out the fine discrimination possible for pain sensation, i.e., twenty-one discriminable steps for a two-fold increase in stimulus intensity. In contrast, the range of energy required to elicit a skin sensation by thermal stimulation beginning at the threshold of temperature or warmth sensation and ascending to the pain threshold is as one is to 2000 (63). There appear to be only about ninety steps of intensity of sensation distinguishable between warmth threshold and the onset of pain. Also, the energy range for vision from the threshold to the dazzle point is as one is to ten billion and there are only 572 distinguishable steps in this enormous range (66).

Certain individuals commonly overestimate the intensity of spontaneously

occurring or experimentally induced pain, but many of these individuals are able, when given a standard painful stimulus, to distinguish various levels of intensity. Although there are some persons who are untrustworthy witnesses of pain intensity, they are identified by their overreaction to non-noxious stimuli and their anxiety concerning or prejudice toward the experimental procedure.

Evidence Concerning Spatial Summation for Cutaneous Pain. There are two aspects of spatial summation. The first which has been reported for vision (61) and for heat sense (62) is that the intensity of sensation from a fixed intensity of stimulus increases or decreases with decrease or increase in the size of the area stimulated. Although experience indicates that noxious impulses may summate under certain circumstances there is at present no quantitative evidence on this point for pain sensation. The second aspect of spatial summation which has been demonstrated for vision (61) and for cutaneous temperature sensation (62) is that the sensory threshold is decreased or increased as the size of the area stimulated is increased or decreased. The usual explanation of this effect is that the sub-threshold impulses from separate end organs are summated in the central nervous system to produce a sensation (35). The significance of spatial summation to the body economy is that it provides extreme sensitivity, thereby permitting sensation to be evoked by minute changes in the environment. For example, vision is stimulated by as little as fifty-eight quanta of energy when the entire eye is illuminated, and warmth sense is evoked by a rise in skin temperature of 0.0008° C/sec. when the entire body surface is stimulated (62).

That spatial summation does not occur when the number of noxious impulses originating in the periphery is greatly increased above the control pain threshold level was demonstrated by the fact that morphine had the same threshold raising effect whether measured in small or in large areas of skin.

For the study of cutaneous pain threshold it was of importance to ascertain whether pain sense exhibited the phenomena of spatial summation. It was observed that within the limits of application of the method, the pain threshold for normally innervated skin was dependent alone upon the strength of the stimulus and not upon the size of the area stimulated, i.e., it was independent of the number of end organs stimulated (36).

Measurements of pain threshold by the radiation technique for areas of skin 0.3 cm.^{2} in size and smaller show an increase in the pain threshold as the area is decreased. This would appear to be evidence of spatial summation of cutaneous pain but careful measurements have shown that due to diffraction and thermal conduction in the skin, the increase in skin temperature produced in such small areas by a specified intensity of radiation is not as great as in larger areas. That is, the limit for comparison of area for the radiation technique is approximately 0.3 cm.^{2} and the apparent spatial summation is actually a measure of the progressive failure of the radiation to raise the skin temperature in such small skin areas. This artefact demonstrates the importance of establishing a known relationship between the quantity measured as the stimulus and its pain evoking action.

Another apparent exception to the concept of non-spatial summation is pre-

sented by subjects who had the number of pain endings in the tissue studied greatly reduced as a result of sensory root section. Thus, in the case of a patient who had his seventh and eighth cervical roots sectioned, the pain threshold was average and uniform on the lateral or normally innervated side of the hand. It was distinctly elevated on the medial portion or that supplied by the sectioned roots. The pain threshold rose abruptly as it approached the most medial portion of the hand and fingers. It is conceivable that the elevated pain threshold in the margin of the nerve-free region is the result of an inadequate density of pain endings in the tissue. It is, however, more likely that the perception of any pain in this area was due to a defect in the method of study, in that the strong thermal stimulus was actually stimulating distant pain endings in the intact portion of the hand through poorly conducting skin tissue.

The importance of the lack of spatial summation is twofold: first, it distinguishes cutaneous pain physiologically from cutaneous temperature sense; secondly, it implies that the intensity of a pain is dependent upon the intensity of the stimulus and not upon the size of the area involved, although the total distress to the individual is dependent both upon the intensity of the stimulus and the size of the painful area and other factors (36, 60).

Moreover, associated with this lack of spatial summation for pain the range of stimuli for producing pain up to the point of tissue damage is small (60). It has been repeatedly demonstrated on the skin that a stimulus twice the pain threshold value causes tissue destruction. In contrast with this is the wide range of stimuli between the threshold for warmth and the pain threshold. It was mentioned that the range of stimulus energy from the excitation threshold of warmth or temperature sensations up to the pain threshold is as 2000 is to one (62, 63). Here spatial summation is of the utmost importance for orientation, and permits a wide margin for discriminative actions of aggression and defence. Through pain the organism is warned of the imminence of tissue damage. There is no need in the body economy for a wide range of experience between the onset of pain and tissue damage since with the first pain impulses the organism receives warning that the limit of safety has already been passed. On the other hand, lack of spatial summation of pain provides that the organism will not be overwhelmed by noxious impulses and so prevented from effective action.

Two Types of Cutaneous Pain. The earliest mention of the view that there are two types of cutaneous pain was made by Gad and Goldsheider in 1892 (67). Since then the double nature of cutaneous pain has been repeatedly explored and although investigators differ concerning whether or not there are two qualities of cutaneous pain or merely variations of one, all are agreed as to the difference in speed of perception. Woollard, Weddell and Harpman (6), Boring (68) and more recently Bigelow, Harrison, Goodell and Wolff (48) are of the opinion that two qualities of pain are involved. Lewis (26) and Gasser (30) are less convinced of differences in quality of sensation but find the difference in the speed of perception of special interest. According to Bigelow, Harrison, Goodell and Wolff (48), one type of pain is abrupt in onset and has a pricking quality which quickly terminates; the other type is slow in onset, never reaches

an abrupt or pricking climax and more slowly recedes. The latter pain has a burning quality whether initiated by pin prick or by heat.

Bishop (69, 70, 71, 72) suggested that "itch, nonpainful prick, and pain, elicited by appropriate patterns of stimulation from the same point differ in quality as well as quantitatively." This qualitative shift with a changing quantity of stimulation indicates, according to Bishop, "a central qualitative interpretation of sensory impulses depending on quantitative factors involving identical peripheral mechanisms within the single modality of pricking pain". It must be pointed out, however, that "stimulation from the same point" is not equivalent to stimulating the same single nerve ending, and therefore does not ensure the implication of an "identical peripheral mechanism" for touch, itch, prick and pain.

Gasser's (73, 74) experiments indicate that the pain first to be perceived when a pin is pressed into the skin or when a finger touches a very hot electric bulb, the so-called "first pain", is carried mainly by the larger medullated fibres conducting at a rate between 10 and 90 metres per second, whereas the slow pain, or that to come on after the above pricking pain has been experienced (so-called "second pain") is carried mainly by small fibres called C fibres at a rate of between 0.6 and 2 metres per second.

Bigelow, Harrison, Goodell and Wolff (48) using the radiation technique studied the difference in properties of these two types of pain. Instead of "pricking" pain endpoint with its final abrupt, sharp-pointed quality, they measured and used the sensory threshold of "burning" pain which was thirteen per cent lower than the threshold for pricking pain for a 5 second exposure to radiation. It had a painful quality which was easily recognized. They showed that this second or burning pain sensation had many properties in common with pricking pain in that the threshold was raised after administering alcohol or morphine, and that no spatial summation occurred when larger and larger areas were stimulated.

Hence, under the circumstances mentioned, there was studied the threshold of another type of cutaneous pain akin, perhaps, to Lewis' "second pain" (26, 75) and conveyed probably by Gasser's "C" fibres (73, 74). The forehead was examined from the point of view of separating these two thresholds and it was noted that over a considerable range in the time of exposure, the pricking pain threshold was appreciably higher than the burning pain threshold. The difference between the two thresholds is more difficult to establish when the tissue is briefly stimulated.

From observations of these two types of pain it became possible to understand certain pathological states. It appeared from studies of pricking pain threshold that there was no lowering of pain threshold in patients with hyperalgesia (76) and peripheral neuritis (48). Indeed, in most instances the pricking pain threshold was elevated. Yet bedside experience forces recognition of the fact that pin prick or manipulation of the skin caused pain at a lower threshold. When such a patient with nerve injury due to a tumor pressing upon the cervical roots, was carefully studied it was demonstrated that the threshold of burning

pain was actually much lower than normal, whereas that of pricking pain, as previously observed, was considerably higher. It would appear that the nerve itself, because of damage, functioned abnormally. Motivated by the experience of Lehmann (77) that faulty oxygenation of nerves might lower their threshold and even cause spontaneous discharges, burning and pricking pain thresholds were assayed in subjects during periods of nerve asphyxia. Such asphyxia was achieved by binding a blood pressure cuff about the arm, inflating it to 200 mm. of mercury pressure and then during the ensuing forty minutes ascertaining the pricking and burning pain thresholds every few minutes in the manner described above.

Following the onset of asphyxia the pricking pain threshold was slightly lowered for a short time and then started to rise and continued to rise rapidly until in about a half hour pricking pain was no longer discernible. On the other hand, the burning pain threshold was lowered for a much longer time so that at the end of twenty minutes it was thirty-two per cent lower than its control level. It was during this period that "hyperalgesia" existed in the sense that a pin pressed into the skin caused burning pain with its characteristic features. This is the period during which Lewis' and Pochin's "second pain" (75) dominates and the "first pain" disappears (26, 75). It is also comparable to that phase of nerve disease during which true hyperalgesia may exist. This may be expressed for superficial pain in the reaction to the pin as just described, and for deep pain by the tenderness associated with palpation of the deep structures.

In summary, then, it may be said that the skin is endowed with two types of apparatus for perceiving noxious stimuli, one giving rise to the quality of pricking which reaches the sensorium rapidly, the other giving rise to the quality of burning which reaches the sensorium less rapidly. The latter is similar to the quality of pain experienced on the glans and on some mucous membranes. This second quality would appear to be an intermediate between superficial and deep pain.

Inference Concerning the "Hyperalgesia" of Peripheral Neuropathy. The sensory changes that occur during ischemia of an extremity resemble in many respects those which occur in the peripheral neuropathy of alcoholism with nutritional deficiencies (78), as well as in other varieties of peripheral neuropathies. Sensations subserved by the myelinated fibres are impaired before those subserved by the unmyelinated fibres.

Wortis, Stein and Joliffe (78) suggested that such "paradoxic pain" results because the loss of one type of pain sensation enhances the perception of another and supported this view by citing Gasser (73, 74), i.e., "that the function of the impulses which run on ahead of the others is to adjust the excitability of the synapses in preparation for the arrival of the later impulses". According to the views of Wortis, Stein and Joliffe, if the impulses from myelinated fibres are lacking, there would be no consequent decrease in synaptic excitability and therefore the neural impulses incident upon the synapses would give rise to more intense sensation. Gasser (73, 74) concerned himself not with sensation, but

with a spinal reflex pattern. He did not infer that a rapidly traveling impulse, as a result of noxious stimulation, alters a synaptic junction for subsequent impulses from the noxious stimulation so that the latter give rise to a sensation of a different intensity or quality.

A further criticism of the view of Wortis, Stein and Joliffe (78) concerning the possible origin of the dysesthesia in peripheral neuritis is contained in the observation of Gordon and Whitteridge (79). The latter have recorded by means of the electroencephalograph the time interval between onset of painful stimulation and disturbance of alpha rhythm of the cerebral cortex. In control observations, the disturbance of alpha rhythm associated with pain from the finger began 0.26 second after onset of stimulation, and following prolonged asphyxia of the finger, the interval between onset of painful stimulation and disturbance of alpha rhythm was 1.02 seconds. Whereas patients with cutaneous dysesthesia accompanying peripheral nerve lesions in the upper extremity demonstrated no abnormal delay, the average time interval between onset of stimulation and disturbance in alpha rhythm being 0.21 second indicating that the fast conducting pain fibres are still active in these patients. Such data fail to support the concept that dysesthesia results from destruction of fibres conducting fast impulses.

The data from the experiments of Bigelow, Harrison, Goodell and Wolff (48) suggest a simpler conception of the "paradoxic pain" of peripheral neuropathy; as the expression of a defect in peripheral nerve, the threshold for "burning" pain subserved by unmyelinated fibres is so depressed that ordinarily innocuous stimuli are perceived as painful, whereas at the same time the threshold for "pricking" pain, subserved by myelinated fibres, is elevated. Under these circumstances, contact with the bed clothes produces a painful burning, and yet pin prick perception is impaired.

Deep Pain—Visceral and Somatic. Since the head (80) and abdomen (81) are responsible for a large share of human discomfort, and, as well, afford examples of two entirely different mechanisms of visceral pain, consideration will be focussed on these structures.

Pain from the head does not emanate directly from the parenchyma of the brain but from its coverings and from its supporting and vascular structures (18). The brain parenchyma and the linings of the ventricles of the brain are insensitive. The analysis of blood vessel pain reveals that a good portion of the pain from the head has its origin in or about these nutrient structures. For analysis of such blood vessel pain from the head, the cranium may be divided into three layers, the most superficial including vessels on the outside of the head, the middle including the dural vessels, and the deepest layer including the pial and cerebral vessels. Postponing consideration of the pain sensitivity of venous structures, that of the deepest layer of arteries may be analyzed first.

It has been possible to demonstrate in conscious and co-operative individuals that the arteries of the brain are pain sensitive in certain regions, notably at the base (18).

Secondly, it has been shown that histamine which widely dilates cerebral

arteries is capable of producing pain (18, 82, 83, 84). The resultant headache has a pulsatile, throbbing quality. It has been demonstrated that it results from dilatation of the cerebral arteries.

It is well known that such indirect effects as muscle ischemia resulting from vasoconstriction may cause pain (26). Also, it is possible that pain may result indirectly from nerve or root ischemia (85). However, with the possible exception of cold pain (86) there is no evidence to show that arterial contraction causes pain directly. Epinephrine, when locally applied to the surface of the pain sensitive middle meningeal artery caused its walls to contract so vigorously that the end result was a vessel which had but a fraction of its former diameter, yet no pain was elicited by such spasm (18). That constriction of cerebral arteries sufficient to impair brain function does not elicit pain was also indicated by patients with scotomata as forerunners of migraine headache attacks (87). Marked visual field defects in such patients preceded the onset of headache whereas overcoming such constriction by suitable vasodilators, when carried to excess, resulted in pain. On the other hand, migraine headaches due to cranial arterial distention were reduced in intensity or abolished by vigorous vasoconstriction as, for example, with ergotamine tartrate or epinephrine (88, 89).

Since blood vessels entering and leaving the brain act in part as supporting or anchoring structures, they may become the origin of pain through traction upon them or displacement. Many such supporting structures have pain fibres on their surfaces. The method of analysis of such deep pain due to traction was as follows (90): A needle in the subarachnoid space was attached to a water manometer. It was then possible to vary at will the pressure within the subarachnoid space, and to estimate the intracranial or vertex pressure. Under these circumstances traction on anchoring venous structures could be induced. Often, pain could be evoked in a subject with increased intracranial pressure by lowering the pressure to normal. Inversely, a headache associated with low intracranial pressure could be reduced in intensity by raising the pressure to normal. Thirdly, headache failed to be induced in normal subjects by raising the pressure eight or ten times above the normal level (91).

Further, it was observed after spinal drainage and tilting of the subject toward the upright position, when the disparity in negative pressure between the intracranial venous pressure and that in the subarachnoid space became sufficiently great, that the cerebral veins dilated and pain was experienced. Increasing the cerebral venous pressure by jugular compression increased the intensity of this pain. Hence, it is necessary to infer that changes in cerebrospinal fluid pressure, per se, are not responsible for headache. The latter has its origin in traction on pain-sensitive vascular structures (90, 91).

The Nonspecific Quality of Deep Pain. Attempts were made to differentiate in the same person the quality of pain: *a*, in headache resulting from intravenous histamine, causing noxious impulses from cerebral artery distention; *b*, in migraine headache emanating chiefly from distended branches of the external carotid artery; *c*, in headache due to venous traction arising after spinal fluid drainage, and *d*, in headache resulting from injection into the frontalis muscle

of a hypertonic salt solution. Although these headaches varied as regards site, pulsatile or nonpulsatile nature and other temporal aspects, and as to whether or not they could be modified in intensity by such factors as position, movement and chemical agents, the quality of the pain was reported to be the same in all. It was of a deep, aching, diffuse nature, quick to arouse reaction in muscles and in glands, such as lacrimation and injection of the eyes, and was associated with feelings of nausea. It was indistinguishable in quality from that which results from painful stimulation of the teeth, the periosteum, or the muscles of the eye (92).

True Visceral Pain. The evidence concerning true visceral pain has been repeatedly challenged since it is difficult or impossible to stimulate one of the visceral organs without at the same time stimulating supporting structures. Mackenzie (93) emphasized that no conclusion concerning pain sensitivity of an organ should be drawn if stimulating pressure is exerted through it against structures which may in themselves be sensitive. Lewis asks whether it is possible that tenderness in patients with gastric ulcer sometimes emanates from the attachments of the stomach to the posterior abdominal wall. Resolution of this question, says he, is important to the problem of visceral pain, for if one admits that true visceral tenderness occurs, then one simultaneously agrees that pain can result from stimulation of a viscus.

The stomach offers an excellent opportunity to resolve the question as to whether or not there be true visceral pain. Wolf and Wolff studied a man who had a large gastric stoma, surgically produced because of esophageal occlusion when the subject was a child. It was observed in this subject that when 50 or 95 per cent alcohol was introduced into the cardiac end of the esophagus it produced a sensation of "heartburn" (81). These observations confirm those made earlier by Jones and others (24, 94) in individuals with intact gastrointestinal tracts.

When the healthy mucosa of the fundus of the stomach was explored through the stoma described above, and the wall of the mucosa was pressed between the blades of a forceps, no pain resulted. Furthermore, faradic stimulation intense enough to cause pain on the tongue, when applied to the fundus mucosa produced no pain. Fifty and ninety-five per cent alcohol, 1.0 N hydrochloric acid, 0.1 N sodium hydroxide or 1:30 suspension of mustard when applied to the mucosa produced no pain.

However, when the gastric mucosa was inflamed, congested and edematous for whatever reason, all of these procedures evoked a pain of considerable intensity.

Whereas mucus is a highly protective substance, the absence of mucus does not explain the change in pain threshold. When the mucus was aspirated away from the normal mucosa, powdered mustard placed on the now dry and unprotected mucosa did not immediately produce pain. It was not until some time had elapsed and the mucosa had become red and edematous that painful sensations could be elicited by pinching or by faradic current. Also, various noxious chemical agents such as 1.0 N hydrochloric acid and 50 and 95 per cent alcohol now became capable of evoking painful sensations.

Thus, although the number of pain fibres and endings may be relatively small, there can no longer be any doubt about true visceral pain originating in noxious stimulation of the inflamed gastric mucosa.

The question whether pain stems directly from the muscularis or rather from the mesentery and visceral peritoneum is less readily answered. Lewis (26), from his summary of available evidence, inferred that contraction of the muscle of the gut does not give rise to painful sensations. It is his opinion that experiments aimed to resolve this question lead to the conclusion that mesenteric attachments are the sources of pain. It is generally agreed that the parietal peritoneum when suitably stimulated gives rise to sensations of pain.

Recent evidence (81) on the aforementioned subject has come from two series of experiments. 1. Ordinarily when the stomach contracts with a force sufficient to support 35 mm. of mercury pain is elicited. When the gastric mucosa is inflamed it required a force sufficient to support only 20 mm. of mercury to produce a similar pain. It may not be inferred from such an experiment that the pain is elicited exclusively from the mucosa. It is doubtful, moreover, whether it represents mesenteric traction since there is less traction as the result of a force supporting 20 mm. of mercury than 35 mm. It seems likely, therefore, that some of the pain emanates from the structures deeper than the mucosa, namely, from the muscularis, the serosa or the visceral peritoneum. 2. When the stomach was stretched by glass rods it was found that when the contractile state of the stomach was average the pressure necessary to produce pain was 100 grams per sq. cm. However, when the stomach wall was strongly contracted pressure of 50 grams per sq. cm. or half that originally applied was found sufficient to produce pain. On the other hand when the stomach was relatively relaxed 150 grams per sq. cm. of pressure was necessary to induce pain. Again, these observations suggest that the muscularis or serosa may contribue to pain experienced from the stomach.

To supplement these observations on the exposed gastric mucosa, indirect but significant evidence comes from the observations of Palmer (95) who has shown that pain from peptic ulcer occurs only when the gastric content is acid. It is reduced in intensity or eliminated by emptying the stomach as by emesis or aspiration, and by neutralizing the acid content with food or alkali. Also, in the patient with peptic ulcer, who is temporarily free of pain, injections of dilute hydrochloric acid (0.25, 0.5 and 1.0 per cent) will induce pain. Pain is not induced by the injection of such hydrochloric acid into the normal stomach or into the stomachs with healed peptic ulcers.

Also, evidence from x-ray examination, according to Palmer (95), demonstrates that the pain of ulcer is not dependent on hyperperistalsis, sustained contraction of the musculature, pylorospasm or distention of the antrum. However, all of these in conjunction with hyperacidity and inflammation augment the pain of ulcer. Thus, peristaltic contractions may induce pain in a patient with ulcer when there is acid present but if the acid is neutralized, peristalsis no longer induces pain. As in the skin and in the mucosa of the bladder and

of the nose, (96, 99) inflammation of the peptic mucosa also lowers its pain threshold (81).

An Analysis of Deep Pain. A conception that aims to organize the data on deep pain must include an appreciation of the following characteristics: associated muscle contraction either transient or sustained, coupled with smooth muscle and glandular effects; deep tenderness; faulty localization of pain; spread of pain; and surface hyperalgesia and hyperesthesia.

a. Rigidity and Tenderness. It is a common observation that deep pain is followed by local and sometimes distant contraction of skeletal muscle (26, 96). The head is a suitable place for the demonstration of such muscle rigidity and tenderness in association with visceral pain (97, 98).

When the pain sensitive structures about the brain or other deep structures of the head are stimulated, the muscles of the head contract. If this stimulus is short-lived, muscle effects are also brief. If, on the other hand, the painful stimulus from deep structures persists, long-lasting contractions of the muscles of the head and neck and even of the jaws and face take place. Such sustained contraction may, in itself, induce pain, and, as well, tenderness of the muscles involved (for example, in certain patients with brain tumor). Recent experimental evidence permits a more precise statement as to the degree and nature of such pain of muscle origin.

Deep noxious impulses with pain from the head cause contractions especially of the frontal, masseter and temporal muscles, greatly accentuate winking and ultimately cause contractions of occipital and cervical muscles. There may also be vasoconstriction or ischemia in the area of muscle contraction. Lacrimation, nasal congestion, edema of the lids, injection of the conjunctiva, sweating and photophobia, nausea and vomiting are common.

Similar contraction effects followed the introduction of a foreign body into the conjunctival sac or on the cornea. They followed diplopia experimentally induced through the use of lenses (19). Long-standing paranasal disease was also associated with sustained painful contractions of the head and neck muscles (97). Muscle pain and tenderness resulted from painful distention and faradic stimulation of the ureter (96). Occasionally after a sustained and painful distention of the ureter, muscle contraction effects increased to such a degree as to become the major factor in the individual's discomfort for as many as twenty-hours. It is thus apparent that noxious impulses, whether they emanate from somatic or visceral structures give rise to the same type of muscle contraction effects, a conclusion originally formulated by Lewis from his experience with abdominal structures and pain (26).

Lewis and Kellgren (28) have demonstrated the non-specificity of such muscle reactions and also how the muscles themselves may become sources of noxious impulses resulting in pain. Furthermore, it has been shown that the pain due to such sustained contraction of skeletal muscle is ended by disrupting the mechanism of noxious stimulation in the muscle by procaine infiltration (97, 98).

Though muscle tenderness is often a sequel of the prolonged muscle contraction perhaps coupled with ischemia, (26, 75) not all subcutaneous or muscle tenderness

has such an explanation. The experiments of Robertson, Goodell and Wolff (41) demonstrate another mechanism of such deep tenderness. After inducing headache, deep tenderness, surface hyperalgesia and hyperesthesia in the temporal region of the head by prolonged stimulation of a tooth, procaine was infiltrated intracutaneously at the site of most intense temporal headache, tenderness and surface hyperalgesia. Within a few seconds after the injection there was analgesia of the skin and the subject estimated that a portion of the headache was eliminated. The temporal muscle beneath the analgesic skin remained tender to palpation. When procaine was injected into the belly of the temporal muscle as well as intracutaneously, pain still persisted although local tenderness was eliminated. However, when the tissue about the noxiously stimulated tooth was infiltrated with procaine, there was complete elimination of all pain.

It is therefore suggested that tenderness sometimes results from central spread of excitatory effects of sustained noxious stimulation. A similar mechanism is invoked to explain surface hyperalgesia and hyperesthesia and is considered further in a following section.

b. Localization and Spread. The localization of deep pain is conveniently studied by stimulation of the nasal and paranasal structures (99). Thus, when the mucosa about the ostium of the maxillary sinus was stimulated either mechanically or by faradic current there resulted at first a localizable intranasal painful sensation. When the noxious stimulation was continued, the subject experienced pain which spread over the homolateral portion of the nose and cheek, along the zygoma, into the temporal region, and into the upper teeth. In short, the pain spread at first from the site of stimulation to predictable sites in the same segment. When noxious stimulation of the turbinates was continued for ten minutes the area of pain spread over most of the area of distribution of the second division of the fifth cranial nerve and ultimately spread to involve adjacent portions supplied by the third and first divisions. This new, more widespread area of pain had a deep aching quality, which became so intense as to minimize the pain from the nose.

The deep aching sensation was associated with blushing of the skin over the cheek, injection of the conjunctiva, lacrimation and photophobia of the homolateral eye. Hence, although deep pain may be initially localized and correctly identified as to site of stimulation, subsequently it may become falsely localized because it is experienced far from the site of stimulation. Also, noxious stimulation of widely separated structures of the nasal and paranasal region caused an identical distribution of pain in remote portions of the face or head. Depending upon the intensity and duration of the painful stimulation the pain may remain localized within the same division or segment, or it may spread so that it seems to emanate from peripheral structures innervated by adjacent divisions or segments.

The localization and spread of pain resulting from stimulation of nasal and paranasal structures are typical of deep pain. Thus, pain from the stomach mucosa, although it is experienced initially as from the stomach itself, subsequently seems to emanate from other parts of the same and adjacent segments.

The latter sensations may dominate so that the initial circumscribed pain is less apparent.

McLellan and Goodell (96) have shown that brief low intensity electrical stimulation of the ureter from within elicits prompt and severe pain experienced along the medial border of the rectus abdominis muscle. Spread from an initially limited portion of a segment to other portions of the segment and then ultimately into adjacent segments was also experienced when the ureter was stimulated at various levels above the bladder orifice. When such stimulation was prolonged or intense, the pain spread so as to include other parts of the segment, beginning on the anterior abdominal wall and ultimately spreading posteriorly. However, the effects of muscle contraction soon masked the initial pain from noxious stimulation of the ureter to such an extent that the entire flank became tender. The muscle contraction then apparently became the dominant source of noxious impulses resulting in pain.

Similar observations were made by Travell, Berry and Bigelow (100, 101) who mapped the distribution of referred pain from noxious stimulation of various muscles. They observed that the referred pain was experienced either within the reference area attributed to one segment, within the different portions of one segment or in fragments of several segments without including any one segment entirely.

With coronary artery occlusion or angina of effort the pain at first seems to emanate from one or more of the anterior portions of the first four or five thoracic segments and spreads headward so as to seem to arise within the structures supplied by the lower cervical, then the upper cervical segments. Ultimately it may seem to emanate from the lower jaw and teeth. The spread of pain so as to include the lower teeth involves the cervical dorsal horn and the descending nucleus of the trigeminal nerve which are contiguous in the upper cervical cord.

To further the study of mechanisms involved in the distribution of referred pain, the commonly experienced "ice cream" headache was analyzed in a subject in whom it was possible to examine separate parts of the esophagus, stomach and mouth (102). It was found that frontal headache developed when the ice was applied to the roof of the mouth but not when a considerable amount of ice was put into the stomach through a stoma, nor when it was held for several minutes in the esophagus. Thus, noxious stimulation of structures supplied by one division of the fifth cranial nerve caused pain to be experienced in structures supplied by another portion of the fifth cranial nerve. Also, but less constantly, pain was experienced in and behind the ear when ice was applied to the region of the fossa of Rosenmuller, and to the posterior wall of the pharynx. These areas are all supplied by the ninth and tenth cranial nerves with possibly a few contributions from the fifth and seventh cranial nerves.

The digits of the hand in certain persons are particularly suitable for the analysis of the spread of pain from a site of noxious stimulation because the pain can be recognized in readily separable zones.

The "cold pain" induced by immersing one digit for 10 minutes in water at

0°C. spreads from the immersed finger to the adjacent border of the neighboring fingers on either side, and may subsequently include the whole of a neighboring finger and a part of a finger beyond.

This pattern of spread having been well defined in 21 experiments in 6 subjects, the fifth finger was anesthetized by a digital block with 2 per cent procaine. The infiltration of the paired dorsal and volar digital nerves was extended to encircle the base of the digit and included dermis and periosteum. The resultant sensory loss in this finger was complete, with absence of superficial and deep pain and of touch, temperature, position sense and vibration sense. When the fourth finger was immersed in water, the spread of pain to the fifth and third fingers was essentially of the same pattern and of the same intensity as in control experiments in which the sensation of the digit was intact. Repetition of this experiment with procaine block of the third finger and immersion of the second in cold water also revealed that there was no interference with the spread of pain into the anesthetic digit. It is inferred that *a*, the spread of pain is a central rather than a peripheral effect; and *b*, that the spread is not dependent upon afferent impulses from the tissues into which spread occurs (103).

Such segmental spread of the effects of noxious stimulation associated with deep pain would appear to be based chiefly on anatomical arrangements within the spinal cord or brain stem. Thus, in one of two similar patients studied by Ray and Wolff (104) severe pain in the right buttock and lower leg, caused by metastatic tumor of the right hip joint and nerve plexus, was eliminated by section of the ventrolateral portion of the cord at the first thoracic segment, on the left side only. After operation, severe deep pain induced by compressing muscles on the left (normal) lower limb or abdomen was felt on the left side only. Similar noxious stimulation of the right hip joint or right gastrocnemius muscle induced a less intense deep pain but also on the left side; the pain was diffuse, poorly localized and widespread, yet mainly in the tissues supplied by the adjacent segments, and it outlasted the period of stimulation by about half a second. Noxious stimulation of low intensity, or repeated pin pricking on the right side gave no sensation of pain on the left. It is postulated from these observations that excitation travels along two possible routes from the primary sensory neurons and their collaterals: 1, the well-known pathway, by neurons in the cord segments of their entry and in adjacent segments that cross to the opposite side and ascend the cord in the spinothalamic tract; and 2, the pathway demonstrated by this patient, that of internuncial neurons that cross in the posterior commissure to connect with neurons on the opposite side of the cord. The latter cross to ascend the cord in the spinothalamic tract on the same side as the entering noxious impulses. Pain is thus experienced on the side opposite to the source of noxious impulses. It is conceivable that the additional synapses necessary for the passage of impulses from the side of entry to the other side of the cord introduces resistance that makes necessary a high intensity of noxious stimulation for such spread of pain to the opposite side of the body.

Included in the evidence of the effects of spread from noxious stimulation on sensory and motor phenomena may be cited the observations of Gellhorn (105,

106) who has shown that spinal reflex movements, as well as those resulting from stimulation of the motor areas of the cerebral cortex are altered during periods of noxious stimulation of either deep or cutaneous tissues. During such noxious stimulation the effect of stimulation of the motor cortex is either intensified or qualitatively altered so that different movements may be substituted temporarily for those obtained under control conditions. These afferent impulses are not limited in their effects to the same side but may also involve the reactivity of the opposite side. Gellhorn suggested that these phenomena result from the cortical spread of excitatory effects, but the evidence for this inference is inconclusive. The effects described in his experiments could be explained by assuming spread at the spinal cord level.

Headache occurs in association with distended bladder in some paraplegic patients with verified cord transection, usually during the first few months following injury. Such headaches are described as throbbing and they may be diffuse, bifrontal, or bitemporal. They are generally accompanied by diffuse sweating and piloerection *above* the level of cord transection as well as below. In most instances the headache is relieved almost immediately after the bladder has been drained. It is likely that such headaches have a vascular mechanism, but the anatomic pathways involved have not been ascertained.

Also, it is difficult to understand on the basis of neural connections the instances presented by Henry Head (107), which involve headache in association with chest disease. Persons with pain emanating from one portion of the chest were reported to have had headaches in one specific portion of the head, whereas those with disease and pain in another portion of the chest had headache in an entirely different site. It is apparent from the case notes that these patients had septicemia or bacteremia and the headache could have resulted from humoral agents acting on cerebral vessels in much the same manner as has been described for experimentally induced histamine or typhoid fever headaches (82, 83, 84, 89). Assuming, however, that the humoral interpretation is valid, the predictable and specific site of the headache is still unexplainable. Others have been unable to confirm Head's observations.

The site selected in the faulty localization of pain appears to depend first of all on the familiarity of the subject with painful experience from a region. Thus, on stimulation of intracranial structures, those near the orbit and those as remotely removed from the orbit as is the superior surface of the tentorium gave rise to pain experienced in, over or behind the eye. If pain be "referred to" or experienced in the part of the segment most accustomed to noxious stimulation it must emanate from the region about the eye since here dust, foreign bodies, drying, inflammation and muscle contraction are common causes of noxious stimulation. It is likely that the cerebral cortex is involved in those aspects of pain that include previous experience or conditioning.

c. Surface Hyperalgesia and Hyperesthesia. On certain portions of the skin, as an accompaniment of deep pain, pin prick may be experienced as sharper and of longer duration, and tactile and thermal sensations seem more intense than those induced by the same stimuli on other dermatomes. Such skin areas

are innervated by the same or adjacent neural segments which supply the deep tissues from which the noxious and painful impulses are originating.

This interesting yet inconstant accompaniment of deep pain has caused confusion and controversy. Though described many years ago (108), the phenomenon was given fresh interest by Weiss and Davis (109). These authors suggested that deep pain could be reduced or eliminated by anesthetization of the associated hyperalgesic areas of the skin. Morely (110) reported that hyperalgesia of the skin over the shoulders from diaphragmatic irritation could be eliminated or reduced by anesthetization of the hyperalgesic area, though Woollard, Roberts and Carmichael (111) demonstrated that the more intense pain resulting from direct phrenic nerve stimulation and experienced in the shoulder tip was in no way influenced by surface anesthetization of this area.

Lewis (26) was not able to modify the pain of angina pectoris by anesthetization of the precordial skin nor was it possible for McLellan and Goodell (96) to alter the pain experience associated with ureteral distention by anesthetization of the hyperalgesic skin area of the abdominal wall. Neither could pain resulting from duodenal distention be modified by anesthetization of the hyperalgesic area in the skin of the abdominal wall (112). Anesthetization of the skin over the calvarium (not hyperalgesic) in no way influenced the intensity of the headache resulting from intravenous histamine injection (113). Also, as mentioned above, (103) anesthetization of the digits in the zone of reference did not modify the pain (see p. 187).

These contradictions are more apparent than real. It was shown by Robertson, Goodell and Wolff (41) that the effect on deep pain of procaine infiltration is related to the occurrence and amount of surface and deep hyperalgesia. Thus, when a tooth was noxiously stimulated causing headache and superficial and deep hyperalgesia of the temporal region of the head, infiltration of procaine into the hyperalgesic skin and underlying soft tissues reduced the amount of discomfort and produced analgesia although it did not eliminate the headache. When the hyperalgesia was more marked the effect of procaine injection was more dramatic. Headache was eliminated, however, by infiltration of procaine into the tissue about the tooth (41). It is, therefore, evident that when pain results from the persistence of primary visceral or other deep noxious stimulation and is associated with hyperalgesia, its intensity may be modified by superficial and deep procaine infiltration in the hyperalgesic zones. However, it is not eliminated until the afferent impulses from the primary sources end spontaneously or are blocked.

The explanation of surface hyperalgesia presented by Mackenzie (93), Ross (114) and Sturge (108) included autonomic afferents and "hyperirritable" foci within the cord. Lewis (26) has postulated that a special nervous apparatus called the noci-fensor system is involved in the phenomenon of hyperalgesia, but anatomic evidence for the existence of such an apparatus is lacking.

It is extremely doubtful that there is liberated in the skin of the hyperesthetic and hyperalgesic areas a chemical agent which lowers the pain threshold (115). Repeated observation of patients with surface hyperesthesia and hyperalgesia

associated with deep pain reveals no significant lowering of the threshold of either pricking or burning pain. On the other hand, minimal pricking and burning pain when they are perceived are experienced as more intense, and seem to be of longer duration. In other words, there is apparently an intensification of the pain perceived at the usual rather than at a lowered threshold (48, 76, 115).

For example, a man with hyperalgesia of the right side of the face, secondary to noxious impulses from deep tissues, was found to have the same pain threshold on the two sides of his face, which was within normal limits. However, a stimulus inducing a sensation which was reported as one plus pain on the control cheek and forehead, induced a sensation which was reported as a three plus pain on the hyperalgesic side of the face. A stimulus inducing a sensation reported as a four plus pain on the control side of the face induced a sensation reported as a six plus pain on the hyperalgesic side. Also, a stimulus of 0.295 gram cal./sec. on the hyperalgesic side induced a sensation which was reported as equivalent in intensity to one produced by a stimulus of 0.335 gram cal./sec. on the control side (115).

If there be liberated into the skin substances capable of lowering the threshold, then the effects of such substances should persist in the skin for at least a short time after the stimulus liberating the substance has ended. To explore this thesis the following experiment was done: An area of hyperalgesia (intensification of prick with pin and touch with cotton wisps) was produced on the skin of the left cheek over the outer edge of the zygoma by placing under the left middle and inferior turbinates an irritating "adrenalin" (Parke, Davis & Co.) tampon (1:1000 solution). The pain threshold for both pricking and burning pain in the hyperalgesic area, as ascertained by the thermal radiation technique, was not lowered. Moreover, when the pain in the face had been obliterated by placing procaine tampons over the irritated surface of the nasal mucosa, almost immediately thereafter the "hyperalgesia" and "hyperesthesia" of the skin was eliminated. In other words, the "hyperalgesia" and "hyperesthesia" did not outlast the period of painful stimulation. These observations make it seem extremely unlikely that a chemical agent was liberated into the skin, which either produced true surface hyperalgesia, or was responsible for the intensification noted (59, 116).

It appears more likely that the intensification of sensation results from a change within the nervous system. It is suggested that the central excitory effects due to the pre-existing barrage of noxious impulses in the segmental or suprasegmental neural apparatus alter the situation so as to make impulses originating at the usual threshold in the skin seem more than usually intense and persistent.

A summation effect analogous to the phenomenon of surface hyperalgesia is encountered in the eye. It is common experience that persons with a cinder in the eye will, on looking into a light, experience the light as momentarily brighter and the cinder as more painful. It is as though a mutual reinforcement of visual sensation and pain occurs (59).

The following experiment may make this more evident (59). There was injected into the muscles of the forehead a small amount of hypertonic saline (0.3 cc. of 6 per cent solution). This caused intense pain. The rate of winking was frequently measured before and after the injection. It was noted that the rate multiplied seven to eight times when the eye was exposed to a light of standard intensity, and dropped to zero when the subject was put in a dark room. Also, immediately after exposure the light seemed brighter than during the control period and the pain in the head due to the salt injection was increased in intensity.

A possible explanation of this phenomenon is as follows: At the segmental level visual impulses entering the colliculus from the retina, exert an excitatory influence on the facial nerve nucleus, causing the increase in winking frequency The spread of the pain from the site of noxious impulses in the muscles of the forehead to other parts of the head results from spread of excitation to involve most of the trigeminal nerve nucleus so that the precise peripheral origin of the pain is no longer certain. Noxious impulses from the head after entering and spreading throughout the trigeminal nucleus exert an additional excitatory influence on the facial nerve motor nucleus so as further to increase the winking frequency (117). The spread of excitation both caudad and cephalad causes the facial, cervical, masseter and temporal muscles to contract. Additional evidence that the motor effects of this experiment are segmental (midbrain or hindbrain) in origin was afforded by some patients with Argyll-Robertson pupil (indicating mid-brain disease). Such persons had faulty or absent wink responses when a strong light was projected onto the retina. Yet they also experienced mutual intensification of light and pain.

The mutual intensification of pain and visual sensations must involve association areas in the cerebral cortex. Nervous impulses from stimulation of the retina by light, entirely separate from those which go to the colliculus, enter the external geniculate body directly. There, through a synapse, secondary disturbances are conveyed to the cerebral cortex. Assuming that current knowledge of neuroanatomy is correct, it is apparent that at neither the brain stem nor thalamic level is it possible for neural activities involved in vision to be influenced or modified by those for pain. Such phenomena can take place at the cortical level only (118). Thus, although reinforcement of the effects of noxious stimuli by non-noxious stimuli does occur within the cerebral cortex, it is also likely that such effects do occur within the cord or brain stem.

To epitomize this analysis it may be said that there are three categories of deep pain:

1. True visceral and deep somatic pain. Such pain is felt at the site of primary stimulation and may or may not be associated with referred pain. It is eliminated by infiltration of procaine into the site of noxious stimulation or by blocking its afferent nerves, but it is not altered by infiltration of procaine into other structures supplied by the same or adjacent neural segments.

2. Referred pain. Such pain may occur in addition to or in the absence of the true visceral and deep somatic pain described above. It is experienced at

a site other than that of stimulation but in tissues supplied by the same or adjacent neural segments. It may occur either with or without associated hyperalgesia and hyperesthesia.

a. Without superficial and/or deep hyperalgesia. In this case pain depends only on the central effects of the spread of excitation of the original noxious impulses to the same and adjacent segments of the cord whence they are relayed to higher centres for perception and interpretation. Injection of procaine into superficial or deep regions of referred pain does not reduce the intensity of pain due to this mechanism.

b. With superficial and/or deep hyperalgesia. Referred pain may be accentuated in intensity by virtue of the effects of ordinarily non-noxious stimuli from zones of reference. Impulses from such sources, normally inadequate to produce pain, may do so upon reaching the cord in a segment involved in central spread of excitation. Procaine injected into superficial or deep hyperalgesic structures will abolish this element of the referred pain phenomenon, resulting in more or less reduction of the subject's discomfort, depending on the amount of hyperalgesia.

3. Pains due to secondary skeletal muscular contractions which provide a fresh source of noxious impulses. Pain may result from secondary effects of the central spread of excitation on the effector structures, including painful contractions of skeletal muscles. Such disturbances may be widespread and the pains may be experienced in situations remote from the original source of noxious stimuli. Local infiltration of the contracted muscles with procaine abolishes this type of pain by disrupting its peripheral mechanism.

Thus in addition to the above described (2*a*) hyperalgesia with unaltered cutaneous pain threshold, there may occur secondarily a deep hyperalgesia with lowered pain threshold in the deep tissues.

The Phenomenon of "Central Pain". The phenomenon of central pain has been but little investigated experimentally. Head and Holmes (119) explained this dysesthesia by postulating the failure of cortical inhibition of excitation within the thalamus, due to lesions that destroyed cortical thalamic connections. Kendall (120) has suggested that the dysesthesia (the phenomenon of "central pain") associated with lesions of the spinothalamic tract and of the thalamus can be interpreted as the result of differential interruption of pathways for afferent impulses inducing pain. He postulates that it is the fast conducting fibres in the spinal cord and in the thalamus which are interrupted by a lesion which leaves intact the slow conducting fibres, the central effects of which, it is further postulated, are normally inhibited by the effects of impulses traversing the fast fibres. The fact that pricking pain is experienced by those with central pain, although its threshold is elevated (48), fails to support such a view.

The Dual Aspects of Pain. The distinction between perception and reaction is apparent and is easily appreciated in the case of heat, light, touch, cold and olfactory perception where the responses are not stereotyped. But when, as in the case of pain, there is an inborn as well as an acquired stereotypy the contrast between perception and reaction is blurred. The reaction pattern of the organ-

ism to noxious stimuli involving pain has many components. It includes "feeling" or emotional reactions, smooth muscle, gland and skeletal muscle effects, and assumes the form of withdrawal, flight or fight.

Instances of the dissociation of pain perception from the pattern of reaction to pain are seen in the indifference to injury sustained during the excitement of games or combat; the apathy, or "quietism" that accompanies tissue damage during certain religious and mystical practices; the indifference to tissue damage during sexual excitement, the indifference to pain often witnessed during parturition in women who are confident in their physician and desirous of bearing a child (14).

Dissociation between pain perception and pain reaction is evident not only after drug administration or during the action of strong beliefs and convictions, but also after cerebral damage. Examples of such dissociation are offered by the experiences of VanWagenen (121) and Watts (122) and of Walker (123). Thus, Walker's patient, a fifty-six year old woman with intractable pain associated with an amputation stump and "phantom limb", had bilateral frontal lobotomy performed for this complaint. In the months following this procedure she was confused but looked content and complained little. When questioned she usually said the arm "pained" but did not volunteer the information. When she was questioned further about the pain she stated that the pain was present but that she gave it less attention and it did not concern her. (See also de Gutiérrez-Mahoney, 32a.)

The dissociation of perception from reaction may be of varying degrees. There may be more or less denial of emotional reactions with repression of vocalization or flight, yet with many visceral reactions sometimes ending in syncope. Indeed, some of these reactions if sustained may damage the organism. For example, G. Wolf (124) has demonstrated that noxious stimuli associated with pain may induce a decrease in kidney blood flow and urine output. Such ischemia is of little importance to the healthy kidney, but in a severely damaged organ, a transient decrease in kidney circulation has resulted in irreversible changes and death (125). Also, Gold, Kwit and Modell (126) have shown that noxious stimuli associated with pain may alter heart function as indicated by the electrocardiogram. Again, such changes, although of little importance to the healthy heart may be of dire significance to one in already faulty function.

Of the various bodily changes available for the analysis and study of such reactions, a sweating and vasomotor phenomenon as represented by changes in the electrical skin resistance has been found useful (17). The point of change in skin resistance resulting from palmar skin changes when the forehead of the subject was exposed to heat radiation, was called the alarm reaction threshold.

Although the pain threshold was constant, the "alarm" reaction threshold varied widely from subject to subject and in the same subject from time to time. It was usually below the pain threshold, although sometimes above it. This reaction is initiated by painful and nonpainful stimuli, when the latter have become symbols of painful or dangerous experience. The reaction or "alarm" threshold differs from the pain threshold not only in its variability but in the

fact that there is spatial summation. Moreover, an analgesic such as alcohol, which has a uniform and predictable effect on the pain threshold, affects the "alarm" reaction in a variable way in the same and different individuals, raising it in amounts from 50 to 800 per cent. The threshold for reaction has been measured by other methods. Chapman et al. (42) using radiant heat to the forehead as a painful stimulus, evaluated a winking response characterized by narrowing of the eyelids as an evidence of reaction to pain. They found that "neurotic" patients in general displayed a lower threshold for reaction than did "control" individuals (127). The older observations of Libman (44) and of Hollander (45) support this view. This reaction component, then, of the pain experience includes the "quale" or feeling state and represents the individual's response to a given situation based on his own past experience and inborn peculiarities. Impressions concerning the rôle of the internuncial neurons in the mechanism of pain in phantom limb and causalgia, as well as their relevance to other sustained states of abnormal reactivity have been described by Livingston (128).

In concluding these considerations, concepts concerning pain may be touched upon again. Until the end of the nineteenth century pain was considered to be exclusively a feeling state. Later, with the discovery of special anatomic equipment and mechanisms, interest was focussed on the perceptual aspects of pain. It then became clear that pain is a specific sensation, and yet, because of its intimate linkage with strong feelings and other reaction patterns, the latter may be dominant in the experience. Reactions to pain may be modified by conditioning experiences and strong beliefs. The common analgesics in addition to effectively raising the pain threshold, also have a major function in changing reactions, attitudes and feelings. Thus, recent evidence supports the old view that the "quale" or feeling state is, to the one who suffers, perhaps the most relevant aspect of pain. Yet it supports as well the conclusion that pain is a specific sensation with its own structural and functional properties. It becomes apparent that these two concepts do not oppose each other: both represent attempts to formulate distinct but fundamental aspects of the pain experience.

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HEAT: MAN'S EXCHANGES AND PHYSIOLOGICAL RESPONSES

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The purpose of this paper is to summarize the applications of physical laws of heat transfer to analysis of thermal relations between man and his environment; to review briefly the important recent work on the physiological responses of man to heat, and to emphasize some of the studies carried out during the war years which have advanced our knowledge in this field. Systematic exploration of the applications of the laws of heat transfer as they apply to man, is not usual in a review which is dedicated to effects rather than causes. Prior to the war there was some tendency to separation of the fields of investigation. The necessities, however, for recommendation on matters of military usefulness required pursuit of both approaches for decision. Recognizing that present knowledge does not permit fully descriptive mathematical expression for thermal relationships and effects, we have nonetheless used what is at hand and attempted to integrate this into the somewhat disrupted pattern which our present knowledge makes.

A complete bibliography will not be presented for reason that much foreign literature is not available and various reports by military agencies remain classified and not accessible. Adequate general reference lists may be found in earlier publications (1, 2, 3, 4) and in the Annual Reviews of Physiology (1941 to 1946).

Military exigencies largely determined the direction taken by the studies of the war years and have emphasized their importance (5, 6, 7, 8, 9). Though man lives and works in all naturally occurring climates, the equipment in military operations (tanks (10), ships (11, 12), airplanes (13)) and the requirements for special clothing, may create local ambient or personal conditions which are intolerable. This, and the need at all times for maximum efficiency in military personnel, have resulted in the greater bulk of the work of the past five years being directed to the following:

A. Extension to extreme ranges of the more precise work of the Pierce Laboratory, Russel Sage Institute, etc.

B. Further attempts to define the upper level of tolerance to heat.

C. Enlargement of studies on acclimatization, its nature, course and duration.

D. Efforts to devise means for evaluation of total thermal stress from known ambient conditions, and correlation of the physiologic responses of man with total thermal stress.

Because of the large number of variables involved and the requirement for immediate answers to problems of military importance, practically all work has been limited to studies on young, healthy men. Little work has been reported on women, children and the aging (14, 15, 16), with only an occasional reference to the unfit or diseased (17). That differences may be great with respect to both tolerance and acclimatization as the result of individual factors, age, or disease,

is a common observation of all who have worked in the field. The important rôle of age and fitness has been commented on (18, 19, 20, 21, 22, 23, 24, 25). The characteristics of military population, their selection, and fitness, and the requirement for limitation of variables in physiological investigation resulted, therefore, in a great deal of work which is of considerable interest physiologically and directly applicable to young, healthy, male populations engaged in specified types of activity. Extension of results to industrial and demographic problems is limited.

MATHEMATICAL CONSIDERATIONS. The physical laws of heat transfer are usefully employed in the analysis of thermal relations between man and his environment. Most of the recent work in this connection stems from the systematic investigations of the Pierce Laboratory.

It is evident, however, that the complex physiological variability of the human body precludes the possibility of formulating rigid equations which fully describe thermal relations under all conditions. Thus, any equation developed by mathematical analysis must be regarded as an over-simplified statement which may fail to predict behavior in individual cases, not because the physical laws are inapplicable but for the reason that all variables are not properly included. Difficulties in this regard are overcome to some extent in experimental work by a statistical approach, working with large numbers of observations on many subjects. In this way, trend lines are established in spite of the scatter of individual observations, from which useful physical constants are derived.

With proper recognition of its limitations as well as capacities, an understanding of the mathematical approach is essential to a thorough analysis of the problem.

1. *Heat Balance Equation.* Mathematical analysis, as developed at the Pierce Laboratory, starts with the basic equation of heat balance:

$$M + D - V = R + C + E$$

where M = metabolic rate
D = rate of change of body heat content
R, C and E = rates of heat exchange with the environment by radiation, convection and evaporation, respectively[1]
V = rate of heat exchange by respiration

The terms to the right of the equality sign may be re-written, in accordance with the established laws of heat transmission, in terms of the *coefficients* of heat exchange and temperature and vapor pressure gradients:

$$M^1 + D = K_r A(t_s - t_w) + K_c A(t_s - t_a) + K_e A(VP_s - VP_a) \qquad (2)$$

[1]Note that D, R and C may have positive or negative values. D (heat debt) is positive when the body is cooling; R and C are positive when the environmental temperatures are less than skin temperature. Note, also, that these are all *rates* of exchange—heat units per interval of time.

where $M^1 = M - V$
A = body surface area
t_s = average skin temperature
t_w = mean radiant temperature of surroundings
t_a = air temperature
VP_s = vapor pressure of water at temperature t_s
VP_a = vapor pressure of moisture in the air (= per cent R.H. × VP at t_a)
K_r, K_c and K_e = coefficients of heat exchange by radiation, convection and evaporation.

The temperature and vapor pressure gradients can be determined by direct measurement. The coefficients, however, are not predictable from physical relationships and must be determined experimentally.

2. *Coefficients of Heat Exchange.* A. *Radiation.* The Stefan-Boltzman equation for heat exchange by radiation applies to man as well as to physical bodies. It has the form:[2]

$$R = KA_r(T_s^4 - T_w^4)$$

$$\text{or } R = KA_r[T_s^3 - 6T_s^2(t_s - t_w) + 4T_s(t_s - t_w)^2 - (t_s - t_w)^3](t_s - t_w)$$

where K = universal radiation constant = 4.92×10^{-8} Cal./M²/hr.
A_r = effective radiation area
T_s and T_w = mean radiation temperatures (absolute) of the body surface and surroundings, respectively.

This equation may be simplified to:

$$R = K_rA(t_s - t_w)$$

where $K_r = K(A_r/A)[T_s^3 - 6T_s^2(t_s - t_w) + 4T_s(t_s - t_w)^2 - (t_s - t_w)^3]$
A_r/A = ratio of effective radiation area to total body surface.

Over a moderate range of wall temperatures, K_r remains substantially constant, the theoretical value ($A_r = A$) being as follows for the assumed values of t_w and t_s:

t_w	t_s	K_r
20	32	5.2
30	33	5.7
40	35	5.9
50	38	6.3

The ratio $A_{r/A}$ has been determined experimentally at Pierce Laboratory (26, 27) and at the Armored Medical Research Laboratory (28), with the following reported values:

Sitting, nude and lightly clothed	0.71–0.75
Standing, nude	0.93

Thus, in a hot environment, a standing man ($A = 1.8M^2$) gains by radiation: $6.3 \times 0.9 \times 1.8 = 10$ Cal./hr. per degree C temperature difference between sur-

[2] Surrounding surfaces are taken to be great compared with man's body area.

roundings and body surface. Heat transfer by radiation is, of course, independent of air movement and, for practical purposes, is not influenced by the moisture content of the air. Against the long wave radiation encountered indoors, ordinary clothing behaves essentially like black regardless of color and, aside from the slight increase in effective radiation area, the effect of clothing upon radiation exchange is negligible. Of the three coefficients of exchange for man, K_r is most firmly established.

B. *Convection.* Heat exchange by convection varies with air movement. Even under still air conditions (no positive air movement, deliberately maintained), natural convection is established around the body and the greater the temperature difference ($t_s - t_a$), the stronger is the air movement, in proportion to the fourth root of the difference. The effect of positive air movement is to superimpose an added velocity effect which, even with low velocities, exceeds the influence of natural convection, so that in an equation expressing the relation between K_c and v, the natural convection component can be ignored. Thus, the simple expression:

$$K_c = K_c^1\sqrt{v}$$

has been found adequate to describe the relationship over a wide range of velocities (15 fpm to 600 fpm). It will be noted that when $v = 0$ in this equation, $K_c = 0$; the velocity, however, is the absolute value and includes natural convection so that, in practice there is no such thing as zero velocity, and heat exchange by convection is never absent (except when $t_s - t_a = 0$). Experimental determinations of K_c have shown that it is highly variable; it varies with body build, the position of the body and for the same measured velocity it will take different values depending upon the direction and complexity of air movement. Under still air conditions values differ because of movement of the subject and variability of natural convection currents. Working with complex vertical air movement around the sitting subject, the following relationship was established at the Pierce Laboratory (27):

$$K_c = 1.04\sqrt{v} \text{ (cm./sec.)}$$

The velocity, in this case, was measured in the empty booth since inconsistent values were obtained when readings were taken in the occupied chamber. At Fort Knox, in a wind tunnel with linear horizontal flow, and with subjects standing nude, the relationship was found to be (28):

$$K_c = 0.74\sqrt{v} \text{ (cm./sec.)}$$

Lack of agreement between the two is accounted for by differences in test arrangements.

The rate of heat loss by convection per unit of body area from light clothing was found not to differ greatly from that of the nude man, despite the greater area of the clothing. This does not hold true, of course, in the case of bulky winter clothing.

In round numbers, a convection coefficient of 2.0 for still air was found by the

Pierce Laboratory. This is about one-half the value of the radiation coefficient. Thus, under comfortable conditions with 25 per cent evaporative heat loss, losses by radiation and convection would be 50 per cent and 25 per cent, respectively. At higher air velocities, however, the proportions are different. At an air velocity of 100 fpm, K_c is approximately 5, and the partition of losses would be: $E = 25$ per cent; $R = 32$ per cent; $C = 43$ per cent.

Compared with K_r, the value of K_c is less well established, although the mathematical form of its relation to air velocity can be accepted.

C. *Evaporation.* Physically, the rate of evaporation from a wet surface varies with the area and shape of the surface, with the vapor pressure gradient and with air velocity. Various empirical and semitheoretical equations have been developed which are helpful in considering human evaporation, but only to a limited extent. These physical equations are for surfaces which are completely and continuously wet—a situation which apparently never occurs in the case of man. As a consequence, the term K_e contains a variable factor of wetted area as well as the others properly included in the coefficient. The degree of wetness varies from a minimum under conditions of normal comfort when no active sweating takes place, up to a maximum value in extreme heat when the sweat rate exceeds the evaporative capacity.

1. Maximum evaporative capacity. The mathematical significance of the evaporative mechanism was developed by Gagge (29), who determined experimentally an apparent maximum value of approximately $K_e = 3.0$ at a single air velocity (8.5 cm/sec., vertical) for sitting subjects (nude) in a moderately severe environment. More extensive data obtained at A.M.R.L., Fort Knox (28) on standing nude men in a linear horizontal air stream gave the following relation between K_e and v for conditions of maximum evaporation:

$$K_e = 1.84\, v^{0.47} \text{ (v in cm./sec.)}$$

At 8.5 cm./sec., the Pierce Laboratory velocity, this gives $K_e = 4.05$, or some 30 per cent greater than the value reported by Gagge. Differences in test arrangements as well as more severe environments undoubtedly account for the higher Fort Knox figure.

The exponential form of the equation is in agreement with the relationships developed for physical bodies such as spheres and cylinders. It is of interest that the coefficient for man is considerably below the values for simple physical bodies, suggesting that even under conditions of maximum sweating, only a fraction of the body area is utilized in evaporation.

2. Less than maximum evaporation. In environments not sufficiently severe to induce maximum evaporation, the sweat rate is adjusted physiologically to an amount which satisfies the heat balance equation. Evaporative heat loss is then given by the equation:

$$E = K_e^1 A(VP_s - VP_a)$$

where $K_e^1 = K_e \dfrac{A_e}{A}$

$\dfrac{A_e}{A}$ = effective evaporative surface, relative to maximum.

The process of adjustment is complex and does not lend itself to direct mathematical description. An increase in skin temperature accompanies the increased sweating rate and thus reduces the heat gain by radiation and convection, which, in turn, lessens the requirement for evaporation. This mutual adjustment continues until a kind of physiological balance is obtained. Under equilibrium conditions, we may write:

$$\frac{A_e}{A} = \frac{M' - R - C}{E \text{ max.}} = \frac{M' - K_r A(t_s - t_w) - K_c A(t_s - t_a)}{K_e A(VP_s - VP_a)}$$

Empirically, $VP_s = 2.5\, t_s - 45$,[3] from which:

$$\frac{A_e}{A} = \frac{M' - K_r A(t_s - t_w) - K_c A(t_s - t_a)}{K_e A(2.5\, t_s - VP_a - 45)} \tag{3}$$

It is evident from this equation that $\frac{A_e}{A}$ is a function of skin temperature as well as of the environmental conditions. As a consequence, the value of $\frac{A_e}{A}$ cannot be calculated from this relationship for a given environment without an independent means of predicting t_s. It is true that t_s does not vary greatly, but even a difference of 1°C in an assumed value of t_s would cause a considerable change in the ratio. For example, assume an environment of $t_a = t_w = 40$°C; $VP_a = 13$ mm; $v = 10$ cm./sec., ($K_r = 5.7$; $K_c = 2.3$; $K_e = 4.3$). For $t_s = 34$°C, $A_e/A = 0.85$. A 1° increase to $t_s = 35°$, however, decreases A_e/A to 0.71, according to this equation. No mathematical means has yet been devised for solving this dilemma.

3. Upper limits of evaporative capacity. In view of the maximum value of K_e, it has been suggested that there are limiting combinations of temperature and humidity (for any given air velocity) for evaporative control beyond which excessive body heating occurs. Using an evaporative coefficient of 3.0 and an assumed constant skin temperature of 35.6°C, such limiting values of dry and wet bulb temperature were calculated (30). It has been found, however, that the skin temperature is not constant under all combinations of thermal stress which elicit maximum evaporation. Hence, the lines thus calculated will not state the case correctly. At $t_a = t_w = 49$°C and $v = 15$ cm./sec. ($K_c = 8.0$; $K_e = 5.4$), for example, we find for $t_s = 35.6$°C that the limiting $VP_a = 11$ mm.; taking $t_s = 37$°C, on the other hand, increases the limiting value of VP_a to 16.9 mm. Thus, by assuming only slightly higher skin temperature, the acceptable moisture content of the air has increased 50 per cent. It is evident that until an independent means of predicting t_s is developed, such calculations are of limited value.

3. *Equilibrium State.* Provision is made in the basic heat balance equation for any changes which occur in body heat content, so that the equation is applicable at all times, whether the subject is in a steady or changing thermal state.

[3] The simple linear equation holds with little error over limited ranges of temperature, such as the range in variability of skin temperature considered here.

When man passes from a normal to a hotter environment, he heats up. Because of his considerable heat capacity and highly flexible sweating mechanism, the resulting increase in body temperature is commonly not great and may escape attention. Nevertheless, there is an increase in body temperature which continues until a new equilibrium is established (provided the subject remains in the environment and his normal physiological processes of thermal adjustment are not altered). Obviously, it is important to know how long a period is required to approximate the new equilibrium state.

The change in body heat content can be written:

$$D = SW(a\Delta t_r + b\Delta t_s)$$

where S = specific heat of body
W = body weight
Δt_r and Δt_s = *rates* of change of internal and skin temperature.
a and b = weighting factors which proportion body heat in relation to internal and skin temperatures.

In terms of the calculus, the heat balance equation can be written:

$$-\frac{SW}{A}(a\,dt_r + b\,dts) = \left[M' + K_r t_w + K_c t_a + K_e \frac{A_e}{A}(45 + VP_a) - (K_r + K_c + 2.5\,K_e)t_s\right] d\theta$$

where dt_r, dt_s = differential changes of body and skin temperature.
$d\theta$ = differential time interval.

Body and skin temperatures are mutually dependent, and, over a limited range we may write: $t_r = m + n\,t_s$, from which $dt_r = n\,dt_s$.

In a given situation, the terms: $[M^1 + K_r t_w + K_c t_a + K_e\,(45 + VP_a)]$ and $(K_r + K_c + 2.5K_e)$ are constant. Calling these C and C^1, respectively, we may write:

$$-\frac{SW}{A}(an + b)\int_{t_0}^{t_e} \frac{dt_s}{C - C'\,dt_s} = \int_0^{\infty} d\theta$$

which gives

$$\frac{t_e - t_s}{t_e - t_o} = e^{-\frac{A\,C'}{SW\,(a\,n+b)}\theta}$$

where t_o = initial skin temperature
t_e = new equilibrium skin temperature
t_s = skin temperature at time, θ.

This equation has the form of the common law of equilibrium and with it, the time required to reach any given percentage of equilibrium can be calculated, provided the values of the several factors are known. It will be noted that the relationship is independent of the environmental temperature, that is, the time required to make 50 per cent (e.g.) of the adjustment to the new environment is the same regardless of the magnitude of shift from one environment to the other.

The rate of body heat production also has no direct influence[4]. On the other hand, the significant factors are: 1, pertaining to the environment: the coefficients of heat transfer, K_r, K_c and K_e, and 2, pertaining to man: heat capacity per unit area, $\frac{SW}{A}$ and circulatory indices, a, b and n. The relationship is comparable to the process of adjustment to an atmospheric contaminant, such as benzol. Continued exposure to the benzol vapor results in a building up of concentration of the contaminant in the body, the rate of increase becoming less as equilibrium is approached. The ultimate body concentration is directly proportional to the atmospheric concentration but the time required to make the adjustment is the same with 1000 ppm in the air as with 10 ppm. The rate is dependent upon the volume rate of breathing and blood solubility (comparable to K_r, K_c and K_e), upon blood circulation rate (compared with a, b and n) and body weight (heat capacity).

Data are limited with respect to the values of a, b and n. For a limited range of exposures for resting subjects, a and b have the reported values: $\frac{2}{3}$ and $\frac{1}{3}$ respectively (31, 32). From A.M.R.L. data, n for standing subjects exposed to heat may be taken as $\frac{1}{3}$. Using these values and assuming an average man: $W = 70\ Kg$, $A = 1.8\ M^2$, $S = 0.82$, we find, for an air velocity of 30 fpm ($K_r = 5.7$, $K_c = 2.9$, $K_e = 5.0$, and $C^1 = 21.1$), the value of the exponent to be $-1.18\,\theta$. Thus, the time required for 50 per cent adjustment is 0.59 hour = 35 minutes and 2 hours—33 minutes' exposure is necessary to attain 95 per cent of the temperature rise to the new equilibrium. At a higher velocity, say 600 fpm ($K_r = 5.7$; $K_c = 13.0$ and $K_e = 15.4$; $D = 58.0$), the corresponding times are: 13 minutes and 55 minutes.

Equilibrium adjustment, as delineated by the above equation is, of course, oversimplified, and ignores certain physiological aspects of the problem to a considerable degree, as will be seen from later discussion. Considering its physical basis, however, it is evidently a close approximation of the true situation, and despite the limited knowledge of the magnitude of certain factors in the equation, especially a, b and n, and the variability of others, the predicted values in the foregoing example are in approximate agreement with experience. Thus, in one of the Fort Knox experiments (33), the temperature rise curves are found to be exponential, in accordance with the equation and to approach equilibrium at the same rate for all environmental conditions, varying from moderate to extreme. These curves yield an average exponent of 1.08 θ, which compares well with the values calculated above.

The time rate of approach to equilibrium is an important factor in designing experiments for the quantitative study of thermal physiology and in the interpretation of results. Experiments of short duration are limited to the steep part of the equilibrium curve where the change in body heat content, D, which can be determined only indirectly, has the greatest value. Observations are the least stable, not only for the body as a whole, but more particularly, from one part to

[4] The ultimate equilibrium level t_e, toward which the subject is tending is a function of the metabolic rate.

another. To illustrate: the specific heat per unit area is much smaller for a leg or arm than for the torso. Thus, other things being equal, the rate of adjustment in the torso is slower. Readings are subject to relatively greater error than under steady-state conditions and may even lead to erroneous conclusions respecting the relative influence of different factors. For example, consider two physically equivalent environments with respect to the combined effects of radiation, convection and evaporation, such that they produce equal skin temperatures at equilibrium, one with relatively still air ($K_r = 5.7$, $K_c = 2.5$, $K_e = 4.4$) and the other with high velocity ($K_r = 5.7$, $K_c = 13.0$, $K_e = 15.6$). The respective values of the exponent in the equilibrium equation would be (for the average man): $-1.08\,\theta$ and $-3.3\,\theta$. Hence, at the end of one hour of exposure, under the still air conditions the skin temperature will have increased only 65 per cent of the ultimate rise whereas with the high wind velocity in the second situation, 96 per cent of the adjustment will have occurred. For a 5° maximum increase, there would be a 2° difference in t_s at the end of one hour exposure, from which it might be erroneously concluded that the two environments were not equivalent.

The concept of equilibrium is important in the consideration of upper limits of tolerance to heat. The statement is frequently made that a given environment. is intolerable because it imposes a thermal demand beyond man's capacity of adjustment and, hence, his ability to maintain a constant body temperature By implication, and often directly, it is concluded that the body temperature will continue to rise so long as the subject remains in the environment. Such a conclusion is erroneous (assuming that maximum sweating rate, circulatory capacity and other physiological limitations are not exceeded). The process of heating up is a temporary one and continues only until a higher skin temperature is reached where E balances $M + R + C$. The equilibrium phenomenon has been demonstrated even in environments well beyond the practical physiological limit of tolerance, involving marked increases in both internal and skin temperatures (33).

4. *Equivalent Environments.* An aspect of thermal physiology of very considerable practical as well as fundamental interest has to do with the question of equivalence of environments. Since the three environmental avenues of heat exchange, radiation, convection and evaporation, are capable of independent variation, it is evident that different combinations can have the same summation effect and thus be equivalent. At the outset, however, in an analysis of equivalence, it is necessary to define the criterion of equality. This has been done in various ways, as: subjective, in terms of relative comfort determined by test subjects (e.g., the "Effective Temperature" of the A.S.H.V.E.); physiological, by an empirical combination of physiological indices (23); physical, derived in various ways from the mathematical equations of heat exchange (30, 34). Each has its own particular advantages and limitations and agreement between them in respect to equivalence of environments is not necessarily expected, owing to basic differences in the initial criteria of equality. Difficulty arises from the fact that two different sets of factors must be combined; not only must the proper

combination of the physical environmental factors be discovered, but also, it is necessary to combine properly a group of complex physiological factors which, together, determine the total strain and which, at the present time cannot be described in absolute terms.

The present discussion will be limited to indices having mathematical origin.

A. *Operative temperature.* Heat exchange by radiation and convection, given by the equation: $R + C = K_r A(t_s - t_w) + K_c A(T_s - t_a)$, may be re-written (34):

$$\frac{R + C}{A} = K_r + K_c\left[t_s - \frac{K_r t_w + k_c t_a}{K_r + K_c}\right] = K_o(t_s - t_o)$$

where

$$K_o = K_r + K_c$$

$$t_o = \frac{K_r t_r + K_c t_a}{K_r + K_c}$$

The combined temperature, t_o, called the Operative Temperature, properly weights the effects of the two elements, R and C, according to their respective coefficients and gradients. Thus, all environments having the same t_o are said to be equivalent in that they impose the same caloric demand by radiation and convection. It is to be noted, however, that this is true only if K_o remains the same. For other K_o values, given by different air velocities, the effect upon skin temperature will be different, necessitating further compensation in environmental temperatures to keep t_s and $R + C$ the same.

B. *Equivalence in terms of skin temperature.* Returning to equation (3), and solving for t_s,

$$t_s = \frac{M'/A + K_r t_w + K_c t_a + K_e \frac{A_e}{A}(VP_a + 45)}{\left(2.5K_e \frac{A_e}{A} + K_r + K_c\right)} \qquad (4)$$

By definition, one could say that all environments giving equal t_s values by this equation are equivalent. It will be noted, however, that the value of $A_{e/A}$ is not definitely known, so that the equation has little practical value until another relationship between $A_{e/A}$ or t_s and environmental stress is developed. In general, it appears that skin temperature increases with air and wall temperatures but for any given combination of temperature and atmospheric moisture content, t_s decreases with increasing air velocity. Thus, it is evident that there is no direct correlation with evaporative demand and sweat output. $\frac{A_e}{A}$ also decreases with increasing air velocity in any given environment below those which elicit maximum evaporation, in accordance with the equation

$$\frac{A_e}{A} = cv^d$$

where c and d apparently vary with environmental temperature and moisture content (or the gradients of temperature and vapor pressure). These indications emerge from Nelson's data (28), which, however, are not extensive enough to permit the determination of the actual values of c and d in relation to the thermal stress.

5. *Physical Instruments for Measuring Equivalence.* Many attempts have been made to develop a single instrument which responds thermally to the environment in a manner corresponding to the human body, thus providing a single equivalent thermal index of the environment in place of the four separate factors: radiant temperature, air temperature, moisture content and air movement. All such attempts have failed for several basic reasons: first, the coefficients of heat exchange of the instrument have not been like those of man, but more importantly, no provisions have been made for equivalent skin temperature variation, which involves in the human body changes in internal conductance and in sweating rate and distribution. With the body coefficients of heat exchange known, it would not be difficult to design an instrument having the same coefficients, but it is not likely that the complex variability in internal conductance of the body and evaporation rate can be duplicated. Thus, it appears doubtful if the objectives of such an instrument can be met. A physical instrument with the proper coefficients and maintained at a selected *average* surface temperature would, however, provide a useful index of the cooling power of the environment although it does not appear that it would provide any basic information beyond that given by separate measurements of t_w, t_a, v and VP_a.

PHYSIOLOGICAL EFFECTS OF HEAT. The heat balance equation given above describes a state. Physiological disturbances in the organism result from increase in body heat content with concomitant temperature rise, and from operation of the homeostatic mechanisms of temperature regulation. Most studies have dealt with measurement of the basic change, i.e., increased internal (rectal) temperature and with the associated effects upon the circulation and volume of sweating, since these are convenient and easily measurable indices of the degree of strain upon the organism. Further evaluation of the physiological effects may be made by means of the appearance and behavior of men, the subjective state, functional efficiency, and the occurrence of heat exhaustion (18, 19, 21, 25, 33, 35, 36, 37, 38, 39, 40). In the interpretation of any observations it is important to keep in mind that the basic physiologic change is an increase of the body heat content associated with the new equilibrium level, and that the capacity of the individual to perform efficiently is the only definitive criterion of overall effect, most other phenomena being evidences of load upon the homeostatic mechanisms. The lack of ability to predict performance on the basis of evidence of circulatory system strain or increase in body heat content alone, has been emphasized (21, 25, 41, 42, 43).

1. *Body Temperature and Gradients.* Since the time of Claude Bernard (44), the temperature of the internal mass of the body has been the subject of speculation and study, and it is recognized that there are local variations in general order and direction of the fluctuations in temperature which change with ac-

tivity, alterations in local circulation, ambient temperatures, time, level of thermal equilibrium, etc. (1, 3, 45, 46). The rectal temperature properly measured has been accepted by practically all workers as the arbitrary index of internal body temperature. Spealman (47), however, believes that temperatures taken within the stomach are possibly a more reliable index of deep body temperature than measurements made within the rectum, because the close proximity of surrounding cold water to the junction of the rectal thermocouple may cause falsely low readings. Our own observations do not support this.

It is to be expected that lags will occur in any changing state. The temperature of the internal organs responds somewhat more promptly to heating and cooling than does the rectal temperature, the temperature of the viscera reflecting the changes in heat production of these organs, and significant thermogenesis occurs in the intestine of dogs (48, 49). In thermoelectric measurements of blood in the aorta, portal and hepatic veins, the lowest temperature was found in the aorta and the highest in the hepatic vein. That the viscera are largely responsible for heat production and that resting muscle contributes little is pointed out by Milhorat et al. (50), who compared results from 50 normal individuals and 100 patients with muscular diseases. In pre-pubertal patients muscular wasting up to 60 per cent had no effect upon heat production and muscle wasting in adults was disproportionally great when compared to slight reductions in heat production that were observed. Barcroft and Edholm (51) found temperatures of from 18 to 44 degrees C in the brachioradialis muscle after immersion of the arm in water from 12 to 45°C. They point out the various factors which determine local temperatures. All of the recent work and earlier analysis (1) lead one to the inference that the concept of a gradient may imply a constancy of conditions which can exist only in highly controlled and constant situations. The thermogeography of the body had perhaps best be looked upon as a series of constantly shifting regional equilibria or exchanges, with differing levels subject to the variables operating at the moment. Considerably more data will be needed before the pattern and order of magnitude of the subsurface thermal shifts can be synthesized.

The frequent employment of skin temperature data in studies of thermal exchange has provided a large volume of new observations, much of which has been integrated into other studies (23, 28, 33, 41, 52, 53, 54). The most satisfactory tool for measurement remains the radiometer as described by Hardy and DuBois (55). As pointed out above, the use of skin temperature alone has limited value in interpretation of evaporative loss.

2. *Peripheral Blood Flow; Vasomotor Regulation.* Earlier definitive studies (56, 57, 58) have established the rôle of dilatation of blood vessels in increasing heat elimination and describe the general distribution of vasomotor changes. Additional comprehensive studies by Sheard (59) and other workers (60, 61, 62, 63) have further clarified the regional aspects of the vasodilatation at temperatures ranging from 18° C to 34°C. They found (as have others) that the regulation of heat dissipation at comfortable environmental temperatures (23 to 30°C) is accomplished chiefly by changes in the tonus of cutaneous vessels in the ex-

tremities. At 18°C the superficial vessels of the head and trunk are already near maximal dilatation while those of the arms and legs still show considerable constriction—the legs more than the arms. Between 18 and 25°C, increase in heat dissipation is brought about by dilatation of the vessels of the arms and hands, and at high temperatures (25 to 30°C) additional loss is accomplished by dilatation of the vessels of the skin of the feet and lower legs. Maximum vasodilatation was maintained at ambient temperatures above 31 to 32°C, evaporative heat loss then meeting additional need for dissipation. In contrast to cooling rates of skin, which were exponential, two rates for warming were obtained, consequent upon the effects of both increasing input (vasodilatation), and environmental gain. Evidence is offered that the arterioles of the skin are capable of dilating as a result of direct effects of heat upon the vessel (63). When conditions are extreme, the central mechanism functions as an integrating agency (as it does in the general response to local heating). This central reaction is mediated by capillary dilator fibres of the sympathetic system.

Other studies (64) have pointed out the ease of producing indirect vasodilatation by heat.

The time required for circulation in the forearm to reach equilibrium at various temperatures is indicated by the studies of Barcroft and Edholm (51) who found at 45°C, that the flow increased to a maximum in from 30 to 45 minutes and remained constant thereafter. These findings are very pertinent in the light of the many observations on the time required to reach a steady state of thermal equilibrium. It would be very interesting to know whether this time for maximum dilatation is shortened by repeated exposure or general acclimatization. The magnitude of the increase in peripheral flow has been investigated (65). Using a combination plethysmograph and calorimeter embracing the hand, flow rates of the order of 30 ml./100 ml. tissue in the hand were found at 38°C as compared with volume flows of as little as 0.15 ml./100 ml. tissue with exposure to cold. The maximum rates of flow were lower than some reported (66, 67, 68).

The results of many workers have established that local temperature changes will incite like general and contralateral responses and heat acts as a coronary vasodilator, the effects being reflex in origin (69). That cutaneous vasodilatation is associated with corresponding changes in muscle is demonstrated (51).

3. *Circulation.* Beginning with exposure and gain in heat storage evidence of strain upon the homeostatic mechanisms becomes evident and there is superficial vasodilatation with increased cutaneous circulation. To compensate for the higher rates of peripheral flow, cardiac rate and output increase, blood pressure rises, and sweating begins (70). With extreme ambient conditions and when the heat dissipating mechanism is unable to maintain the body temperature within the limit that is critical for the individual, physiological breakdown occurs. The manifestations are diverse, the outstanding exhibit being inadequacy of circulation with a forward type of failure. Taylor, Henschel and Keys (71) reported results of 7,000 observations on pulse, blood pressure, rectal temperature and rate of sweating of 43 subjects—before and during exposure to dry heat for from 2–8 days. Modified Crampton scores were calculated and the devia-

tions from control values noted. Bean and Eichna (21, 25, 72) have described the cardio-vascular instability in detail and elsewhere Eichna et al. (33) present in tabular and graphic form observations on rectal temperature, heart rate, sweating and skin temperature for a group of 13 experimental subjects exposed to environments ranging from 92.4 to 96. T_w(T_d 92 to 120°F.). The point is made that changes in the circulation do not always parallel or indicate the capacity for overall performance. They noted in their study of more difficult environments (T_w 94 and T_d 94 to T_w 91 and T_d 119.3) that some of their subjects experienced an adjustment like "second wind". During the first hour men worked with difficulty and had heart rates that tended to be higher than expected (an increase of about 25 beats/degree C rise in rectal temperature), while toward the end of the second hour men improved and were in better condition. Decrease in heart rate, despite a rising rectal temperature, occurred in some men in the second hour. Disturbances were most pronounced during the changing state—subjects achieving thermal equilibria for the test environments in about two hours.

A. *Instability of circulation.* Associated with the very considerable shifts in circulation a degree of instability becomes evident. When the stress is great, or after some hours of exposure, especially with work, instability may become pronounced and its effects disabling (21, 23, 25, 71, 72). The instability becomes especially apparent in the upright position, a result of inability to achieve postural adjustment. The circulatory effects of the vertical stance have received much study and have been reviewed (73), and recent work under ordinary thermal conditions has been reported (74, 75). Allen, Taylor and Hall (76) found that 20 per cent of 111 young men developed orthostatic insufficiency on the tiltboard at normal temperatures. These rates are like those of Eichna's (72) group of 150 men, 23 per cent of whom had orthostatic hypotension with syncope on initial exposure to heat. An additional "abnormal" group (21 per cent) included subjects who could remain erect for 3 minutes but whose blood pressure was below 100 mm. Hg and at least 10 mm. below levels under comparable conditions in the cool. After 5 days of work in the heat, only 1.0 per cent of men fainted when tilted and 13 per cent fell into the normal group. Thus, 5 days of repeated exposure and training reduced the percentage of men with some degree of circulatory system inadequacy from 44 per cent to 14 per cent. Allen (76) likewise found that training developed the ability to withstand gravitational stress. Interestingly enough he found that this capacity was not related to the ability to meet the stress of vigorous exercise. It would be helpful to have more information upon the relationships between the ability to withstand orthostatic stress in the cool (with and without work) and the capacity to maintain adequate circulation in the heat.

The reasons for the poor return are not clear at this time. It is known that there is increase in the capillary bed with venous enlargement and relaxation and arteriolar dilatation is perhaps a critical factor (77). That venous pooling with reduction in venous return does occur seems inescapable, and additional data on the magnitude of reduction in venous pressure produced by trapping of the blood in the extremities have been reported (78). The ability to prevent syncope in the

erect position by initiation of limited muscular activity in the legs, the application of cuffs, and the common observation that elevation of the legs will prevent the fall in blood pressure, are all in support of the thesis that circulatory inadequacy is associated with pooling of blood in the extremities and deficiency in venous return. At high temperatures the disturbances, however, comprise much more than a simple disparity between the capacity of the vascular bed and the available volume of blood. We have, unfortunately, no electromyographic studies in heat. Warmth relaxes voluntary muscle and one suspects that lessening in muscle tone with reduction in pumping action (79) may contribute significantly to failure of adequate venous return.

Added loads other than posture have been investigated in relation to thermal stress and numerous reports have pointed out the deteriorating effects of heat in the presence of shock-like states (80, 81, 82). Whether induced by hemorrhage or burns, high environmental temperature has a decisive influence in increasing mortality. In this connection, the disturbances in thermal regulation that occur in congestive heart failure are of great interest. Heat production may be increased in heart failure, but observations in cool climate (83, 84, 85) suggest that the high body temperature results from disturbances in circulation to the skin with resulting impairment of heat loss.

B. *Adequacy of circulation.* The adequacy of circulation is contingent upon a number of factors, important among which are the relationship between the blood volume and the capacity of the vascular system, and normal functional ability to increase cardiac output by increase in rate and stroke volume. Even with adequate venous return, relationships between pulse rate and cardiac output are complicated and with exposure to high temperatures with great demand for peripheral flow and additional inadequacy in venous return, it becomes impossible to evaluate the significance of individual physiological changes as isolated phenomena. The initial and often considerable elevation in pulse rates can give quite an erroneous notion as to cardiac output and adequacy. Pulse rates per degree increase in rectal temperature vary rather widely (from 20–30/min.) but are considerable. Pulse rate and blood pressure are indices of the strain on the circulation rather than of the ability to control rise in body temperature. The general relationship is obvious, but not sufficiently close to be of value in individual instances. As Krogh (86) has observed, with an inadequately filled heart an increase in pulse rate from 75 to 120 would result in a decrease in cardiac output from 3.1 to 2.9 liters. These factors and the marked influence of muscular activity upon venous return, account for the differing statements as to the effects of heat on cardiac output. Wilkins, Hunt and Friedland (87) reported only minor changes in cardiac output with warming and cooling, which was attributed to the buffering capacities of the circulatory system. Earlier observations have established that with initial exposure, at least, there is some increase in cardiac output. Asmussen (88), working with acclimatized subjects, found no significant differences in output in the first half hour of work, after which there was decrease in output, more marked in the hot climate than in the cool. As work was continued and breakdown began, a reduction in stroke volume of 20 per cent associated with very high pulse rates was noted.

Glickman et al. (89) reported results on studies of blood volume as affected by heat. Increase in plasma was noted in 6 experiments, decreases in 4 and no change in 14. Increases that were noted ranged from 5 to 13 per cent. In instances where there was no change in plasma volume the red blood cell volume increased. Reports on blood volume changes continue to be confusing. With respect to Glickman's observations, it may be noted that exposures were quite short (a few hours) and hydration was not maintained. When adequate time is allowed blood volume increases up to 20 per cent or more may be observed (53).

One can think of few things which do not affect the blood pressure—high ambient temperature is no exception. In general, significant deviations are not observed except during the changing state and during the period of instability in the first few days of exposure to high temperatures when there is a tendency to low values especially in the erect stance and precipitate drops may occur before the syncopal attacks. The fall may be in the systolic, diastolic, or pulse pressures (21, 24, 25, 72).

4. *Sweating.* The subject of insensible water loss has been reviewed. Little new has been added since by way of basic concept. Barbour (91), in summarizing his studies of water movement in response to environmental temperature, emphasizes the heat-conserving properties of vapor pressure changes as they affect the availability of fluid for insensible loss and sweating.

Pinson (92), in study of water loss in skin areas in which the sweat glands had been inactivated, found that general exposure to heat caused increases in water loss, insensible perspiration being doubled by an increase in skin temperature of 10°C. Rate of blood flow acted only as it increased the skin temperature.

The variations in rate of sweating in different parts of the body have been studied under subtropical conditions (93). The most rapid rates of insensible loss were from the hands and feet, forehead, and cheeks, the loss being relatively slow from the trunk, arms, and legs. Marked variations from area to area occurred. In experiments carried out under extreme conditions very high rates of sweat loss have been reported (23, 33, 41, 52). Under severe conditions a sweat loss of 2.25 L/hour was common (33). The magnitude of the fluid exchange is apparent from these estimates. With an average man having 3.5 L of plasma (of which 3.2 L are free water), men lost an amount approximating 70 per cent of the free water of the blood. In some instances the subjects lost from 3.3 to 3.9 L of sweat an hour, representing amounts equalling or exceeding (120 per cent) the total blood water. Under the experimental conditions the maximum sweating rate was 4.2 L/hour and some men completed 4 hours of work while sweating at rates of 3.0 L/hour (amounting to 4 times the blood water and about $\frac{3}{4}$ the total extracellular fluids). The significance of these high fluid losses will not be considered here in relation to the problem of fluid balance, save to say that with adequate replacement there were only small changes in cellular volume and in the concentration of electrolytes, decreases in serum sodium, potassium and chloride concentrations being less than 5 m. Eq./L (33). The rôle of evaporative loss has been commented upon above and the problems of relating coefficient of evaporation, skin and air temperature and wind velocity pointed out. The mechanisms for control of sweating have been studied (94),

and the ability of denervated sweat glands to respond directly to heat and mecholyl demonstrated (95). Remote responses are however dependent upon the intact state of the motor side of the reflex arc. The sensory side was found not to be necessary since general sweating followed the action of heated blood upon the central nervous system.

Though the limiting capacity of the circulatory system is usually the determining factor, failure of the sweating mechanism may limit adjustment to heat. Collings (96) found cessation of sweating a prodroma in 26 per cent of cases of heat exhaustion in steel mill workers. Others (40, 97, 98, 99, 158) describe cases of failure of sweating mechanism designated as "thermogenic anhydrosis". The phenomenon was seen after prolonged exposure to desert climates; or it followed exposure to hot humid heat for 7 months (98). The regional distribution of the anhydrosis was similar among the cases and like that which follows thoracolumbar sympathectomy. Since sudomotor, pilomotor and vasomotor responses may be governed by the end organ, sweat gland, vessel, or pilomotor muscle, by reflex through the spinal cord, or by central hypothalamic control, the location of the dysfunction was sought (99). Response to heat, pilocarpine and mecholyl was one of complete anhydrosis in the affected area, with hyperhydrosis above. Recovery was prompt in the cool, when repeat test elicited normal response. Despite the fact that cholinergic drugs failed to evoke sweating, it was not believed that the end plates were the site of involvement, since mecholyl, etc., fails to stimulate sweating in cerebral lesions, heat stroke and thyroid crises. Action is viewed as an active cerebral inhibition which is sufficiently strong to abrogate drug effects. A refractory state of the sweat gland itself has not been excluded (151, 152, 153).

The disastrous effects of heat on patients having hereditary ectodermal dysplasia of the anhydrotic type is well known. Studies of the effects of heat on 2 of 3 brothers without sweat glands have been reported (100). Regional variations in water loss were further studied in diseased subjects (101, 157). The existence of great variation in water loss in the absence of disease was evidenced by one subject, clinically well, but who complained of undue fatigue when working in hot weather. Skin water losses under comfortable conditions (75°F., R.H. 50 per cent) were consistently below average normal, the difference being markedly accentuated in hot, humid conditions (105 T_d, 75 per cent R.H.). A more recent contribution (17) demonstrates that the deficiency in circulation associated with congestive heart failure, results in a reduction in sweating to from 27 to 47 per cent below normal levels for the patient during the compensated state. The deficiency was general, and even mild thermal stress was poorly tolerated by these patients.

5. *Salt Depletion.* Questions of salt requirement, methods of maintaining electrolyte and water balance and the effects of water deprivation will not be considered in this report except for mention where they have a direct bearing upon the effects produced by heat.

That high rates of sweating result in the loss of large amounts of salt and lead to a deficiency state with characteristic disturbances has been well established

(102), and recently, the salt deficiency states have been excellently portrayed (11). The important relationship of salt intake to cardiovascular function and heat exhaustion received limited attention until the investigations of Taylor, Henschel and Keys (41). In a study of 34 subjects, they demonstrated that a moderate salt intake is essential for the maintenance of cardiovascular function and the prevention of heat exhaustion. Men on low salt intake (6 grams) had higher pulse rates and rectal temperatures than did men on normal (13–17 grams) intakes. A significant observation was that salt deficiency with reduction in plasma chloride was not always associated with heat cramps but in many instances led to heat exhaustion. Failure to replace water leads to similar phenomena of dehydration exhaustion (18, 19).

Recent opinion as to salt loss during exposure to heat is summarized in a report of the Council of Pharmacy and Chemistry (103).

Studies of Pitts et al. (104) led to results like those of Taylor, and indicate that while water replacement was best on an hour to hour basis, special circumstances are required to justify salting of the water. They suggest that the chloride concentration of sweat is affected by 3 primary factors: 1, a peripheral factor correlated with skin temperature; 2, a central one correlated with rectal temperature and rate of sweating, and 3, personal idiosyncrasy. They found the rate of sweating and salt content to increase with increasing rectal temperature. Taylor et al. (41) found no correlation, and Horvath and Shelley (52) observed increasing rates of sweating with unchanged rectal temperatures. Consistent differences between subjects have been observed by all investigators. Morreira, Johnson, Forbes and Consolazio (105) found that chloride changes followed the foregoing pattern of responses (104) and that sodium was present in concentrations almost equivalent to chloride and showed the same correlations with skin and rectal temperatures and with rates of sweating. In contrast with sodium, sweat potassium invariably decreased as work was prolonged and showed no correlation with the factors listed above.

6. *Metabolism and Nutrition.* Studies of resting metabolism in the heat are complicated by many factors and results are far from consistent; elevations, depressions, and no change having been reported. Too many studies neglected the factor of acclimatization and the level of thermal equilibrium at the time. There appears to be little question that during the changing state, before acclimatization, and when the rectal temperature is elevated, significant increases in resting metabolism occur and that these increases are in general in accord with the Van't Hoff coefficient (106). After acclimatization, however, low levels are a more uniform finding (107). A detailed account of the course and magnitude of the lowering in resting metabolism has been reported (108). In contrast to the above, others (21, 109) found no change in basal metabolism after from 5 to 10 days' work in the heat; the subjects, however, exhibited elevations in rectal temperature at the time.

A. *Caloric requirements and specific dynamic action of proteins.* No great differences in the caloric requirement of man occur as the result of high temperatures. Studies on rats have indicated a lessened requirement at high tempera-

ture as evidenced by greater weight gain with similar intake and activity, and study of the voluntary food intake of United States soldiers did not reveal any measurable seasonal differences (110). This is in harmony with the observations that no significant changes in efficiency of working metabolism as a result of heat are demonstrable at high rates of caloric expenditure. Any differences that might be expected to result from the lessened requirement for heat production per se, would be quantitatively insignificant in relation to the overall expenditure. Similarly, any heat production from the specific dynamic action of proteins is of no consequence. That it moreover is not measurable has been shown (109).

B. *Vitamin requirements.* The situation as to optimal intake of vitamins and the benefits of supplements has been greatly clarified. Mills and colleagues (111, 112, 113, 114, 155) believe that there is increased requirement in the heat with increased need for choline (5 x normal). It is doubted that these results are valid as applied to man. Well-controlled human studies by others (109, 115, 116, 117, 118, 119, 120, 121) offer convincing evidence that there is no increase in requirement or benefit from added supplements of vitamins or choline.

Whether inferences as to requirement may be drawn from excretion levels alone is doubtful. Dietary intake is but one facet of a figure which comprises need, intake, absorption, distribution, utilization, excretion, etc. With clinical observations valid for at least the duration of the studies, one is led to the conclusion that isolated observations on animals and on excretion, etc., are interesting but not definitive with respect to man.

The possibility of increasing the ability of man to work in the heat by means of administration of specific substances has been attractive. The results are disappointing (122, 123). Many of the symptoms of heat exhaustion are like those of adrenal insufficiency (124). This, and other reports (125) on the beneficial effects of adrenal cortex in hyperthermia led to its trial in men working in hot environments. No consistent effects were noted (97, 105).

7. *Gastro-Enteric Tract.* The anorexia, nausea, vomiting, cramps and frequent diarrhea that often occur during high heat stress, reveal the pronounced effects which heat may have upon gastro-enteric tract function. Explanation for the occurrence of these phenomena is not complete. The vomiting has been explained on the basis of rejection by the stomach of fluid that is not being absorbed because of limitation in blood flow to the stomach (88). Henschel et al. (24) studied the gastric emptying time of 17 normal men at temperatures of from 77 to 120°F. In all but 1 the gastric emptying time was faster at the higher temperature; in 12 of the 17 a decrease of 30 per cent in time was seen at the higher temperatures. A study of 100 men doing hard work at 120°F. failed to reveal any anorexia or decreased gastric activity except when actual heat exhaustion occurred.

8. *Thermal Regulation.* Thermal regulation continues to be a matter of great interest and has recently been reviewed (3, 46, 126, 156). Further light upon the factor of chemical regulation is offered in the report of Hardy (15). Other reports (46, 127) have been concerned with the character of the nervous control and thyroid activity. A significant paper covering clinico-pathologic studies of

disturbances of temperature regulation in man has been presented by Davison (128). Four cases of hyperthermia and one case of hypothermia were studied. In three cases of hyperthermia the lesions responsible were sharply circumscribed in the ventromedial tuberal nuclei in the floor of the 3rd ventricle.

9. *Acclimatization.* Man is a homothermic animal capable of great increases in internal heat production. He, moreover, lives in a constantly changing thermal environment, all of which requires continuous regulation to maintain thermal equilibrium at his normal level of internal temperature. Even short bursts of work with its high heat production or minutes of interference with heat dissipation (hot rooms, excess clothing, etc.) will increase heat storage and elevate internal temperature (154). With sustained increased level of heat production or continued interference with dissipation, a new level of thermal equilibruium is established by the individual. As this is repeated or continued for days there is rapid acquisition of the ability to maintain the same or lower level of thermal equilibrium under the same conditions of stress, at less cost to the individual. When the shift in temperature is moderate, the initial load on the homeostatic mechanisms is minimal and often unnoticed. Slight increases in rectal temperature and pulse rate are nonetheless usual (129). When the change is great, and to an environment of high thermal stress, with initial marked physiological effects, the subsequent improvement in performance and reduction in load upon homeostatic mechanisms is spectacular. This acquired capacity entails complex readjustments, the mechanism for which is often conjectural. It has been suggested that shift of vasomotor control to thalamic centers is entailed (22). Without regard to hypothesis, the process of acclimatization is characterized by certain phenomena and changes which have been well studied and described in investigations carried out within tolerable thermal limits (21, 23, 24, 25, 33, 41, 130, 132, 133).

A. *General state.* Beginning with the first day and continuing at a decreasing rate for from 8 to 10 days there is progressive improvement in the appearance and behavior of men. Incidence of heat exhaustion, headache, dizziness, polypnea, gastroenteric tract symptoms, inco-ordination, irritability and depression decrease progressively. Most of the improvement occurs in the first 4 or 5 days and when acclimatization is achieved the subject will often perform as willingly and well in the heat as was formerly possible under temperate conditions.

B. *Circulation.* Circulatory system instability which is closely related to the production of many of the above symptoms, follows the same general course during the acclimatization (21, 33, 41, 71, 72, 131). Changes in heart rate are dramatic, the principal reduction occurring in the first 4 or 5 days.

C. *Rectal temperature.* The general course of the rectal temperature is progressively downward during acclimatization, the reduction being more gradual than that of changes in circulation or performance. At low levels of heat stress, normal levels may be reached in from 7 to 10 days—in general, levels of from a few tenths to a degree or more above normal still are encountered after 10 days.

D. *Sweating.* Rates of sweating uniformly increase during acclimatization

though the magnitude of increase is widely variable. Increases in rates of sweating usually begin later (after from 3 to 5 days) than do other changes and may continue longer and even augment later (41, 52). The lack of relation between this phenomenon and the mean skin and rectal temperatures was demonstrated in Horvath's (52) study of 16 men acclimatized to severe conditions (T_w93°F.). Chloride concentration tends to decrease during acclimatization (134) except in the presence of exhausting work.

There has been good agreement among most observers that the performance and appearance of men, degree of vascular instability, cardiac rate and rectal temperatures when evaluated together, are so closely related to the state of acclimatization as to comprise the most reliable indices of the state.

The practical limits of work and environment for which acclimatization can be achieved are reviewed below. Limits for acclimatization are not only sharply defined but the adjustments involved in the acclimatization are easily disturbed. Thus, a fully acclimatized man may exhibit any or all of the disturbances characteristic of the unacclimatized state if excessive rates of work are imposed (21, 23, 24, 33, 71, 135) or if there is intercurrent infection (7), loss of sleep, or alcoholic indulgence (21, 33). More importantly, failure to maintain complete hydration (18, 21, 25, 136), caloric intake (120) or salt intake (11, 41, 104) will lead to prompt deterioration in performance. The same factors which enable good performance in the cool and which are related to good initial capacity to perform in, and acclimatize to heat, are similarly important to the maintenance of the acclimatization. The acclimatized state is not only unstable with respect to the above factors but is also a temporary adjustment in that it persists for a limited time only. With reduction in thermal stress, acclimatization is lost more slowly than it was acquired, the rate being influenced directly by the magnitude of the difference in the ambient temperatures (21, 24). A good state of acclimatization is maintained for 1 or 2 weeks with gradual loss thereafter; some men retain a fair degree at the end of 2 months. In studies in the winter months persistence for at least 3 weeks is usual (71). Repeated exposures at least 1 month apart are required to maintain good acclimatization (21).

E. *Factors influencing acclimatization.* A number of factors influence the ability to acquire acclimatization and the rate of its development. Resting in the heat is associated with a limited adjustment, but work within limits of tolerance is necessary for full development. Exposure and work in hot, dry environments results in a partial acclimatization to hot humid conditions. Repeated brief (1½ to 3 hrs.) daily bouts of work in the heat will acclimatize men but fullest adjustment is attained most quickly by graded, progressively increasing work in the heat.

After acclimatization to one level of thermal stress, further acclimatization may be acquired for more severe environments (23, 33), and acclimatization to a high level of heat stress enables greatly enhanced performance in less severe heat (52).

Long-term changes have not been studied under controlled conditions though the performance of men after months or years of work and residence in environ-

ments of high thermal stress is a matter of great practical importance and short-term studies cannot be expected to elucidate these slowly changing factors. These may be associated with deterioration, rather than improvement in adjustment and performance (4,137,138). Several reports (97,98,99) have called attention to the instability of the sweating mechanism that may appear after months of residence in the heat and Collings et al. (96) noted stoppage of sweating in 26 per cent of steelworkers prior to breakdown—many of the men having had years of exposure. Certainly when the stress is high, deterioration can occur in a matter of hours or days (151, 152, 153). The character of the changes at low orders of stress maintained for years is not indicated. Investigation of the problem of deterioration is most urgent.

10. *Work in Hot Environments.* Work in hot environments imposes two additive stresses, increased internal heat production, and added demands upon the circulation for the supply of muscle. Determinations of the relationship between the stresses of ambient conditions, work and dehydration have been reported and reviewed (19, 133, 137, 139, 140).

11. *Upper Limits of Tolerance.* All of the factors which influence environmental stress, heat dissipation, heat production or the fitness of the man, become qualifying variables in any attempt to define limits of adjustment. In addition, the criterion of limit may range from discomfort to death. The relative significance of certain of these factors has been studied and referred to above: Environmental; air temperature, water vapor in air, duration of exposure, air movement, radiation, clothing, constancy of stress. Individual; diseases, work, body size, acclimatization, age, fitness, individual variation, posture, fatigue, water balance, salt intake, caloric intake, alcohol. It is apparent that the large number of variables will limit the application of results of particular experiments rather narrowly to the conditions and types of subjects employed. A further complication arises in definition of limit of tolerance. Should some level of performance be employed or should the convenient indices of pulse and rectal temperture be used? If the latter be employed and we accept the rectal temperature during the steady state as the index of the existing level of thermal equilibrium, one faces the question of what constitutes an acceptable range of increase in levels. Certain limiting values have been proposed (23, 133, 140). Attempts to relate psychophysiological performance to ambient conditions and to level of rectal temperature have not yielded very promising results (141).

Studies of Eichna et al. (33) have established a series of environmental conditions at which sustained work (4 hrs., at 250 cal./hour) is easily possible, difficult or impossible as a day-to-day performance for periods up to one week. Their subjects were well trained, fully acclimatized, young men, and were maintained on adequate salt and water intakes. They found, as had Haldane, that the T_w was the most important factor in determining the upper limits of tolerance and a better index of climatic stress up to 120°T_d than was T_d or the effective temperature. At T_w up to 91°F, men worked easily and efficiently, maintaining thermal equilibrium with rectal temperatures under 101°F. Between this tolerable ambient level and T_w 94°F (above which sustained work was impossible),

work became progressively more difficult and heat casualties occurred with increasing frequency. There is general agreement as to the level of tolerable T_w. In 1909 Haldane (142) set the upper limit of tolerance for resting men in still air at T_w 90°F as did McConnell, Houghton and Yaglou in 1924 (35). Other reports (30, 38, 143, 144) arrived at similar limits. The agreement in level is in general fairly good, but not perfect. Robinson (23) reported a series of 212 experiments carried out at temperatures ranging from 23 to 50°C with various humidities. His subjects maintained work at metabolic rates of 130 cal. M^2/hour at 35°C with 96 per cent relative humidity and were in thermal equilibrium from the second to sixth hours of exposures at 34°C with 91 per cent relative humidity. The ability to maintain thermal equilibrium was taken as the criterion for tolerance. We believe that the maintenance of equilibrium is a good measure of the capacities of the homeostatic mechanisms but is not itself a measure of limits of tolerance since new thermal equilibria may be established at any level within the ability of the individual to withstand the thermal stress.

Search has continued for means of evaluation of total thermal stress in terms of known ambient conditions and the correlation of values obtained with physiological effects. Robinson (23) arrived at an index of physiological effect of environment from weighted data on heart rate, skin temperature, rectal temperature and rate of sweating. This he designated as E_p or index of physiological effect. Using this index, environmental conditions which resulted in equal E_p values were determined and are presented in graphic form. Differences in behavior of clothed and nude men are given. With severe thermal stress Robinson's contours parallel those of Houghton and Yaglou (145) for effective temperatures. In comparison with the results of Gagge, Harrington, and Winslow (30), Robinson's contour line extrapolated to 100 per cent relative humidity, is about one degree higher at saturation with about the same air movement.

Plummer, Cochrane and Siple have developed a similar concept, designated as "Thermal Acceptance Ratio" (54). Methods of evaluating environmental loads are presented. Like other approaches, this requires the assumption of a skin temperature and makes no provision for the complex factors involved in sweating and evaporation. Since the stress imposed by an environment is a function of the ratio between the ability of the environment to take up heat and the requirement for heat output by the body, considerably more information is needed before refined general expressions will be entirely acceptable. A considerable advance in defining relationships has been made by Nelson and coworkers (28).

Much-needed observations on the effects of high levels of radiation gain have been reported (135, 146, 148, 149). The increases in metabolic rate caused by radiation are significant.

12. *Heat Disease.* In heat stress, either by reason of the direct effect of high levels of thermal equilibrium or because of overstressing of homeostatic mechanisms, performance may quickly deteriorate and collapse occur. Again, with high stress, there may be a gradual deterioration in work capacity with the appearance of distressing and incapacitating symptoms. With this breakdown,

and without regard to type of onset, there appears a train of physiological disturbances which, when taken together, make up the clinical syndromes of heat cramps, heat exhaustion, and heat stroke. The syndromes are descriptive of the final states encountered and are practically useful in determining therapy; physiologically their occurrence throws light upon the character of the breakdown of the overstressed homeostatic mechanisms. The conditions encountered clinically have been described in detail (11, 36, 37, 39, 40). The most spectacular of these syndromes, heat stroke, is characterized by coma, hyperpyrexia, cessation of sweating and circulatory failure. Levels of hydration and salt content are normal and extreme levels of rectal temperature (108–112°F.) are encountered. The second type, commonly differentiated into 2 syndromes, heat cramps and heat exhaustion, appears to have a common basis, the pattern of symptoms being determined by the relative importance of the effects caused by circulatory system instability, salt deprivation, and dehydration (11, 41, 96). The importance of cessation of sweating has been pointed out above—it is frequently associated with impending failure or stroke and may cause collapse with or without hyperthermia. The question of fatigability of the mechanism has been investigated; the experiences in the field suggest this is an important consideration and the reduction in capacity with time or excessive load of the homeostatic mechanisms is demonstrated in the studies of environments of high thermal stress (23, 24, 33, 151, 152, 153).

Local metabolic and functional abnormalities may result from altered hemodynamics, deficient blood supply, or from the direct effect of temperature itself. Additional evidence of the damaging effects of heat upon the brain have been reported (147). Oxygen uptake of rat cerebral cortex was found to be greatly reduced at temperatures of from 40–47.5°C (104–116°F.). The rate of utilization decreased more rapidly with time as the temperatures were increased, becoming asymptotic at a level 10 per cent of that of control slices at 37.5°C. In about half the experiments the oxygen consumption was constant for an hour or more, in the remainder there was decrease with time beginning as early as 30 minutes after thermal equilibrium. The inhibition was reversible after 3 hours' exposure at 40°C. (104°F.) but after even 30 minutes' exposure at 40.8°C. (105.4°F.) or higher, recovery was incomplete after cooling. Temperatures higher than 41°C. resulted in progressively less complete recovery. These findings are consistent with reports of sequelae following hyperthermia. These have been reviewed (150).

SUMMARY

No conclusions are drawn but the general pattern of the investigations prompts certain comments.

The researches of the last few years have demonstrated that the performance and state of man in relation to his environment is a measurable phenomenon with qualitative aspects often quite dissimilar from the measurable differences in the components that together make up the whole. Man as a functioning organism is quite different in character than any of the systems into which, in an

analytic approach, he may be resolved. The lesson for physiologists is clear; the overall performance of the integrated being should be the point of departure for research endeavors, and the yardstick by which the individual results are gauged. Both types of activity are essential—it is only by splitting off bits that it becomes possible to provide the bricks for building, and only by continuing and related study of the overall performance do we provide the observations necessary for definition of the individual problems, and the architecture of the whole.

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THE DEFINITION AND MEANING OF pH

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This is intended to be a critical review of the meanings that are attached to the term "pH". Some of the principles underlying the methods of measuring it are discussed, but not their experimental details.

There is need for a review of this sort since "pH" may bear several different meanings and since, in spite of its universal use, it is clear that many of its users are not aware of this fact. It may be an exact or inexact statement of the result of a given method of measurement; it may represent an exact physicochemical quantity; often it is used in senses which are physicochemically inexact and ambiguous.

The object of this review is to examine the possible meanings of "pH" and their respective usefulness in the light of well established physicochemical principles. A convention of expression is suggested which should promote clarity and prevent confusion.

I. *Bulk Phases.* pH is most commonly used as a term of description for ordinary bulk solutions. It may serve two rather different purposes: first, to define empirically a unique property of a solvent mixture (including buffer and neutral salts etc.) which shall determine the state of dissociation equilibrium of any given acid dissolved in it, in such a way that the same state of dissociation can be reproduced at will: secondly, to form part of an exact physico-chemical expression of the state of dissociation.

The importance of the hydrogen ion as a factor controlling the dissociation of acids and bases in solution was recognised when Arrhenius applied the law of Mass Action to ionic equilibria. Later it was realised that many substances of biological importance are weak acids or bases whose degrees of dissociation in part determine their biological activity.

In the modern terminology of Bronsted (1) and Lowry (2), any acid-base equilibrium may be expressed as

$$A \rightleftharpoons B + H^+$$

where A and B are conjugate acid and base and H^+ represents, in aqueous solution, the ion H_3O^+. Application of the classical Mass Action theory gives

$$K = (H^+) \cdot (B)/(A) \qquad (1)$$

Sørensen (3) introduced the term pH as a convenient shorthand for $-\log(H^+)$; equation (1) is transformed to

$$\mathrm{pH} = pK + \log (B)/(A) \qquad (2)$$

The use in this sense of pH was typographically convenient; it allowed the whole range of solutions, from strongly acid to strongly alkaline, to be expressed on a compact graphical scale; equation (2) gives the useful symmetrical dissociation,

ionisation or titration curve and furthermore shows that pH defines the value of $(B)/(A)$ for a given value of K.

However, it became evident that equation (1) is not a generally valid expression of acid-base equilibria; the values of K were found to vary with concentrations of the acid-base system and of neutral salts. G. N. Lewis (4) therefore introduced the concepts of "activity", a, and "activity coefficient", f. In ionic solutions these are usually related by

$$a = f.c$$

where c is the concentration; f is defined as approaching unity at infinite dilution and at finite concentration is given such values as to make the value of K equal to that expressed in terms of concentration at infinite dilution. Equation (1) becomes

$$K = \frac{a_{H^+} \cdot a_B}{a_A} \text{ or } \quad K = (H^+) \cdot (B)/(A) \times \frac{f_{H^+} \cdot f_B}{f_A} \tag{3}$$

We shall use the second form in the further discussion.

The logarithmic form of (3) analogous to (2) is

$$\log K = \log (H^+) + \log (B)/(A) + \log \frac{f_{H^+} \cdot f_B}{f_A} \tag{4}$$

It contains four terms in place of the three of equation (2). The "p" notation has purposely not been used because there are two questions which first require answers:

1. Can equation (4) be satisfactorily reduced to three terms, by incorporation of the activity coefficients in one or more of the other terms, so that it becomes like equation (2)?
2. What are the quantities in equation (4) that are measured by the means used for measuring "pH"?

These questions should be considered together because it is desirable that the result of an experimental determination of "pH" should correspond with one of the terms of equation (4) or of a modification of it.

Consider first the ways in which equation (4) might be reduced to three terms.

1. The activity coefficients might be distributed amongst the other three terms, but this may be done only in certain ways. Guggenheim (5) has shown conclusively that the activity or activity coefficient of a single sort of ion cannot be unambiguously measured or defined; this applies more generally to any function

$$\frac{(f_{x\cdot})^m (f_{y\cdot})^n (f_{z\cdot})^o \cdots}{(f_{x'})^{m'} \cdot (f_{y'})^{n'} \cdot (f_{z'})^{o'} \cdots} \tag{5}$$

such that the algebraic sum of the ionic charges of $x, y, z \cdots$, each multiplied by its exponent *minus* that of the charges of $x', y', z' \cdots$ is not zero. The attachment of any numerical value to such a function must involve some arbitrary assumption; and while the use of such a function may sometimes be con-

venient, it is easy to overlook the fact that an implicit assumption has been made and, consequently, to become involved in an argument which can lead only to that assumption, perhaps in a disguised form.

The charge of B is always one unit more negative than that of A. It follows that there are only two cases in which the division of the activity coefficients is legitimate; that in which A carries no charge, when it is permissible to separate $f_H{}^+ \cdot f_B{}^-$ from f_A, leading to

$$pH = pK + \log \frac{(B^-)}{(A) \cdot f_A} \tag{6}$$

where $\mathrm{pH} = -\log(H^+) \cdot f_H{}^+ \cdot f_B{}^-$;
and that in which B carries no charge, which leads to

$$pH = pK + \log \frac{(B) \cdot f_B}{(A^+)}$$

where $\mathrm{pH} = -\log(H^+) \cdot f_H{}^+ / f_A{}^+$. (7)

These two definitions of pH correspond with the quantities that are obtained in certain measurements and will be discussed further.

One definition of pH is often used which is quite illegitimate; this is

$$\mathrm{pH} = -\log(H^+) \cdot f_H{}^+ \tag{8}$$

Authors frequently refer to the "activity of hydrogen ion" or the "activity coefficient of hydrogen ion" apparently thinking that they are being peculiarly precise and unaware that they are using terms which are physically undefinable and whose magnitudes are experimentally unmeasurable, unless some special arbitrary assumption is made about the magnitude of some other quantity in the system.

One such assumption may perhaps be justifiable, namely that the properties of any ion depend only on its charge. This may be approximately true in the range of concentrations to which the Debye-Hückel treatment applies, though even in such dilute solutions the radii of the ions have some effect. The mean activity coefficient of any uni-univalent electrolyte may then be defined as

$$f_+ \cdot f_- = f_\pm^2$$

and

$$\mathrm{pH} = -\log(H^+) \cdot f_\pm$$

This is sometimes a useful convention; but it should be recognised as being arbitrary.

2. The activity coefficients might be combined with K to give a modified, variable "constant". But this is not in accordance with common practice which is to define K as a constant of the acid-base system and to give it a value measured under specified standard conditions, which include the temperature and the solvent.

3. The activity coefficients might be combined with $(B)/(A)$ so that we should write

$$\log K = \log (H^+) + \log \frac{(B)}{(A)} \cdot \frac{f_{H^+} \cdot f_B}{f_A} \tag{9}$$

There is no objection in principle to this, but it is not very useful. Where an indicator or buffer is used, it is the ratio $(B)/(A)$ that is measured or fixed; where the behaviour in this solution of another electrolyte is considered, the activity coefficients of its ionic forms and of those with which it interacts are required for the description, not those of B and A. The third term of equation (9) does not therefore supply all the information that is required for such description and equation (9) offers no advantage as compared with equation (4).

4. The activity coefficients might be combined with $\log(H^+)$ to give

$$\log K = \log (H^+) \cdot \frac{f_{H^+} \cdot f_B}{f_A} + \log \frac{(B)}{(A)}$$

or

$$pH = pK + \log (B)/(A) \tag{10}$$

where

$$pH = -\log (H^+) \cdot \frac{f_{H^+} \cdot f_B}{f_A}$$

This also is theoretically unobjectionable. It might be positively justified if it could be shown that this function is given directly by the practical means for measuring pH. We shall proceed to examine these.

There are two general means of measuring pH: by the observation of chemical equilibria and by measuring the EMF of an electrolytic cell.

1. *Chemical equilibria.* There are three methods of measuring or fixing pH which all yield the same sort of function of concentrations and activity coefficients.

a. A buffer is used to fix the pH by fixing the value of the ratio $(B)/(A)$ in equation (4). Given the value of K of the buffer, the pH obtained directly is that of equation (10).

b. An indicator is added to a solution whose pH is fixed but unknown and the ratio $(B)/(A)$ of the acid and basic forms of the indicator is measured. Given the value of K of the indicator, the pH obtained is that of equation (10).

c. The rate of a hydrogen ion-catalysed reaction is measured. This is determined by the concentration of the complex A formed between the substrate B and the hydrogen ion

$$H^+ + B \rightleftharpoons A$$

The ratio of rates in two solutions thus measures the ratio of concentrations of A in them: the pH difference measured is that of equation (10).

2. *Potentiometric methods.* There are two sorts of cell used:

a. Cells with liquid junction. The type of cell most often used consists of a hydrogen or glass electrode dipping into the solution, with a calomel reference electrode

connected with the solution by a salt bridge; the "liquid junction" occurs between the salt bridge and the experimental solution. This type of cell has the great disadvantage that, in whatever way the liquid junction is made, the processes at it are irreversible and are not therefore subject to thermodynamic theory. Guggenheim (6) concluded that their EMF can be described only in terms of the mobilities and concentrations of all the ions present in all parts of the cell and our present knowledge does not allow this to be done more than very roughly. Obviously such a cell can give no theoretically satisfactory measurement of pH.

b. Cells without liquid junction. Cells of this type consist of two reversible electrodes dipping into a single solution. Their EMF can be precisely described in thermodynamic terms. Such a cell would consist of a hydrogen or glass electrode with, perhaps, a silver-silver chloride electrode reversible to Cl^-.

$H_2 \cdot Pt$/Solution containing buffer and neutral salts including H^+ and

$$Cl^-/AgCl \cdot Ag$$

The EMF of this cell at standard pressure of hydrogen gas is given by

$$E = E_o + RT/F.\ ln(H^+)(Cl^-) \cdot f_{H^+} \cdot f_{Cl^-}$$

where E_o is the EMF of the cell when it contains HCl of activity defined as unity. Since the concentration of Cl^- can be estimated chemically, one might define pH as measured by the EMF of such a cell containing unit concentration of Cl^-.

$$\text{pH} = -\log(H^+) \cdot f_{H^+} \cdot f_{Cl^-} \tag{11}$$

The reference electrode might be reversible to some other cation such as Na^+; then its EMF is given by

$$E = E_0 + \frac{RT}{F} \ln \frac{(H^+) \cdot f_{H^+}}{(Na^+) \cdot f_{Na^+}}$$

and one might define

$$\text{pH} = -\log(H^+) \cdot f_{H^+}/f_{Na^+} \tag{12}$$

From the foregoing discussion it appears that none of the definitions of pH is uniformly satisfactory. Those that are obtained directly from a method measurement (equations 10, 11 and 12) have the disadvantage that the quantity measured contains not only a quantity characteristic of the solution, but also quantities which are characteristic of the measuring system. Thus different measuring systems applied to the same set of solutions will give different results. For example, two indicators will in general record different differences of pH between the same two solutions and this will be especially marked if the indicators are of different ionic charge type; two different buffer systems, especially if they are of different ionic charge type, will suffer different changes of pH with change of ionic strength; two cells without liquid junction which have different

reference electrodes will respond differently to the same change of ionic strength. Nor can it be argued that the activity coefficients which refer to the ions of the measuring system will be valid for another system in whose dissociation we may be interested; this will be true (and even then only approximately) only if this system is of the same ionic charge type as the measuring system and only in dilute solutions.

Thus if it is desired to give an exact description of the state of dissociation of a given solute in a given solvent mixture, in relation to a measured property of the solvent, it is necessary to measure or compute both the activity coefficients relevant to the measuring system and those relevant to the solute. No advantage is to be gained by an attempt to reduce equation (4) to three terms and it is better to let the activity coefficient term stand explicitly alone. This means a return to Sørensen's original definition of

$$pH_S = -\log(H^+)$$

which is the only function characteristic of the solvent mixture and independent of the solute or measuring system. This is distinguished by the subscript S (denoting "Sørensen") from any empirical meaning of pH. It would prevent confusion if pH_S were used exclusively in would-be exact physicochemical expressions and reserved for this purpose.

At the same time "pH" as commonly used is very useful within certain limits. It does provide an easily made measure of the physico-chemical state of a system which enables that state to be approximately reproduced from one experiment to another. In solutions fairly dilute with respect to electrolytes and in which specific interaction of ions is small, the activity coefficients of different salts and uncharged species do not differ very much from each other or from unity and the estimates of pH of such solutions obtained by different methods—even from cells with liquid junction—will not be widely different; this is true even if it is difficult to interpret the measurement in terms of exact physico-chemical quantities. In quoting such a pH value it is important to state the method by which it was obtained; for example, the buffer mixture or indicator, the assumed value of pK, the concentration of neutral salt, the electrode system and the standard of pH used to calibrate it. Indeed, it is often more precise and no more trouble to state the composition of the solution alone; for example, to state that a protein was dialysed against "$NaCl$ 0.2M, Na_2HPO_4 0.1M, KH_2PO_4 0.1M" rather than "0.2M phosphate pH 6.8 containing 0.2M $NaCl$".

To summarise, it is highly desirable that pH should be confined to two meanings:

1. The ordinary empirical quantity used as an approximate specification and derived directly from a method of measurement; in quoting its value, all the relevant details of the method should be given. It should be written "pH".

2. In any exact physico-chemical expression where its use is desired for brevity, it should mean only $-\log(H^+)$ and should be written "pH_S". Activity coefficients should appear explicitly as a separate term, as in equation (4).

II. *Bulk Phases in Membrane Equilibrium.* Bulk phases separated by a membrane which allows the passage of some but not all of the ions deserve some special discussion; differences in their properties are of interest in accounting for the differences of composition across natural membranes, for example, between the interior of a cell and its surrounding fluid. Since each of two phases considered is a bulk phase, there might seem on the one hand to be no need to add to the foregoing discussion; on the other hand, since they are in equilibrium, it might be tempting to give a thermodynamic rather than a stoichiometric meaning to pH and to say that it ought to be taken to be the same in both the phases.

However, it is not legitimate to use any such concept as "activity of hydrogen ion", which can be measured or defined only relative to some arbitrary definition. What can be measured is either physically indefinite or involves other ions as well, depending on the method of measurement. Thus, as in the case of single bulk phases, the values obtained depend on the method of measurement and the activity coefficients which their expression involves are relevant only to the particular method used.

1. *Equilibrium methods.* Owing to the Donnan equilibrium effect, the distributions of ions of different charge type will differ. Thus the values of $(B)/(A)$ for a buffer or indicator will be different in the two phases; the values will depend also on the ionic radii and on factors leading to specific interaction between ions. The ratio of the values of $(B)/(A)$ found in the two phases with a given indicator are the same whether the indicator species are themselves in equilibrium across the membrane, provided that they can pass through it, or whether small amounts of indicator are added to separated samples of the phases. A solution obtained by dialysing a charged colloid against a buffer is not identical with that obtained by dissolving the colloid in the same buffer, even if the colloid is first adjusted so that it will not appreciably exchange ions with the buffer system.

2. *Electrode systems.* The passage of current between two electrodes, one being in each phase can lead only to:

a. The transfer of combinations of ions satisfying the condition of electrical neutrality (5), if the electrodes are reversible to ions that can pass the membrane.

b. To polarisation of the membrane if the electrodes are reversible to ions that cannot pass the membrane.

c. More complex changes if the electrodes are not reversible.

Of these, *b* will give no useful information while *c* will be difficult to interpret. *a* is represented, for example, by a pair of hydrogen or silver chloride electrodes, one in each phase; the potential difference between such a pair is zero. Similarly, the potential differences between a reversible hydrogen and a reversible chloride electrode, both in the same phase, are the same in each phase. These identities correspond with the identity of the activity of any combination of ions, that satisfies the condition of electrical neutrality, in the two phases. On the other hand, the potential difference between two calomel-KCl electrodes, one in each phase, is not zero; nor are the potentials of hydrogen against calomel-KCl measured in the two phases the same; the reason for these differences must

lie in the irreversible nature of the processes that occur at the liquid junctions of the calomel electrodes.

There seems to be no reason, therefore, to vary the conclusions reached for the case of single bulk phases. In using pH in its empirical sense, it becomes even more important to specify the conditions of its measurement. For exact expressions the use of pH_S is desirable, which leaves the effects of activity coefficients and of Donnan distribution to be expressed explicitly.

Membrane potentials. Appeal is often made to an electrical potential difference across the membrane to explain the unequal distribution of given ions. The difference of potential between two calomel-KCl electrodes, one in each phase, is often taken as measuring this potential. Since use is made of this potential in connection with observations on the osmotic pressures of solutions of charged electrolytes and their "pH", the matter requires some attention.

The derivation of the Donnan distribution does not require the assumption of any membrane potential; only two conditions need be imposed to obtain it:

1, that both phases shall be electrically neutral;

2, that the activity of any combination of ions, whose transfer across the membrane involves no net transfer of charge, is the same in both phases (e.g., a pair of oppositely charged univalent ions).

All the properties of the system, including the osmotic pressure, can be expressed in terms of the stoichiometric concentrations of ions in the two phases and the activity coefficients of salts and there is no need to assume any value of potential at the membrane to account for any of these measurable quantities.

There is no doubt that there does reside in the membrane a discontinuity to which the name "potential" can be given. But any definition of its magnitude must involve the work of transfer of a single sort of ion from one phase to the other; this involves an assumption about the activity coefficients of that ion in the two phases which, as has been seen, must be arbitrary. The case is exactly that of the potential of a single electrode against solution. The stoichiometric ratios of concentrations of different ions in the two phases will in general be different so that there can be no unique standard even of arbitrariness. The membrane potential could be used only to give an account of the stoichiometric ratios, but it is preferable to deal with these directly and explicitly. The membrane potential is, therefore, a useless abstraction.

The quantity measured as the "membrane potential" is usually the potential difference between two calomel-KCl electrodes, one in each phase. While this is a reproducible quantity, under given conditions of experiment, its measurement involves the use of two liquid junctions of KCl solution against solutions of different composition. The assumption that the whole—or any definite part—of the observed potential difference arises at the membrane is completely arbitrary and any attempt at testing its truth must involve an arbitrary assumption about the activity coefficients of some one sort of ion.

The use of the concept of "membrane potential" is therefore to be avoided. If any assumption has, for convenience, to be made, it is much better based on a ratio of concentrations than on measurements with calomel electrodes.

III. *Interphases.* The state of dissociation of an acid group in an interphase is often different from the state of dissociation that it has, or from its chemical nature would be thought to have, in a bulk phase in equilibrium with the interphase. Such a difference is of interest to the biologist in connection with the properties of proteins and other colloids and of cells. It is desirable that such differences should be expressed in satisfactory terms.

Interphases differ in some important respects from bulk phases. They are the regions of discontinuity between bulk phases. They are very small in bulk and are anisotropic. Care is needed that terms applied to them shall be physically definite and can be related to measurements that can actually be made on them. Thus, to consider, as Craxford, Gatty and Teorell (7) do, the readings that might be obtained with electrodes placed in the interphase is not helpful, because it would not be possible to know in practice in what part of the interphase the electrodes had been placed nor what disturbance they might have introduced; nor can analytical measurements be made on an interphase. The only properties of an interphase that can be measured are those relative to the bulk phases; for example, interfacial tension (that is, the change of energy of the system on increasing the area of interphase), electrophoretic mobility or streaming, or the changes in the composition of bulk phases that result from the formation of interphase. The state of dissociation of groups in an interphase can be deduced from measurements such as the change of interfacial tensions over a solution of a fatty acid or amine with pH of the bulk phase (Peters) (8), the change of electrokinetic properties with change of composition of the bulk phase (Danielli) (10) or the changes in the colours of indicators in the presence and absence of interphase.

Without for the moment specifying the meaning of its terms, acid-base equilibrium in an interphase may be stated to be expressed by an equation analogous to (4). In comparing such an equation with that applying to the bulk phase, special care will be needed about the meaning of "concentration". Only the Gibbs "surface excess" Γ of any molecular species can be measured; this may be positive or negative and its difference from zero certainly implies a difference of something resembling "concentration" between interphase and bulk phase. But the interphase is anisotropic and even an average concentration cannot be obtained from Γ unless the thickness of the interphase is known. The thickness is usually unknowable and therefore subject to arbitrary definition; only in certain rather simple cases can any quantity be obtained which is in any way analogous to thickness. These are the cases where the A and B forms of the substance or group in whose dissociation we are interested are materially confined to the interphase; that is, in which the surface excesses of A and B are very large and positive, compared with their concentrations in the bulk phase. Such cases are those, for example, of monolayers of long-chain fatty acids or the surface of particles of protein. The degree of dissociation in the interphase can then be sharply distinguished from that in the bulk phase, since the bulk phase contributes negligibly to the quantities of A and B in the interphase; the other particles in whose distribution we are interested are then ionic and their dis-

tribution is largely determined by electrical forces arising in the interphase. We shall confine attention to interphases of this sort.

Now consider equation (4). Since A and B are materially confined to the interphase and only their ratio enters the equation, these can be defined in any convenient way, such as quantities per unit area of interphase. The activity coefficient term is dimensionless. It follows that K and (H^+) are of the same dimensions. Therefore, if K is to be of the same dimensions as in the bulk phase, then (H^+) must have the dimensions of a volume concentration; or if (H^+) is to have other dimensions, such as a surface excess, then K must be correspondingly defined. But, in the latter case, the value of K would not be comparable with that in the bulk phase and it would be necessary to refer all thermodynamic quantities to a standard state defined for the interphase, which would be experimentally inconvenient. We shall therefore keep K having the dimensions of a volume concentration.

In terms of equation (4), the observed differences of $(B)/(A)$ in interphase and bulk phase could be described in three ways, which we shall discuss in turn:

1. *Difference of K.* One would expect the tendency of an acid molecule to dissociate to be different in an interphase and a bulk phase; not only may there be an electrical potential gradient in the interphase, but other physico-chemical conditions also may be considerably different, such as dielectric constant and the basic strength of the solvent. Hartley and Roe (9) suggested a difference of K as a means for expressing the difference of degrees of dissociation in interphase and bulk phase in equilibrium. This is certainly permissible and might at first sight appear particularly reasonable. But it must be remembered that K may be given any numerical value whatever according to the definition of a standard state. A rational definition of K in the interphase would be with reference to some accessible standard state in the interphase, but this has the disadvantage which has been mentioned that all measurements on an interphase are in fact made relative to a bulk phase. Hartley and Roe choose as a standard state in the interphase that in which there is no gradient of potential; while this allows the Debye-Hückel treatment to be applied to the variation of K with composition of the bulk phase, the standard state cannot be even closely approached in many cases. In view of the fact that, in any case, the numerical values of K are subject to the definition of the standard states and therefore do not measure the difference of the tendencies of an acid to dissociate, it seems simplest to retain the bulk phase value of K for use in the interphase.

2. *Difference of* (H^+). There will certainly be a surface excess of hydrogen ion in the interphase, positive or negative, according to the electrical and other physical properties of the interphase. Insofar as it depends on the electrical properties, the Debye-Hückel theory allows this surface excess and its distribution in depth of the interphase to be calculated in simple cases. The influence of other physical factors cannot be allowed for, so that a calculated value of the surface excess and its distribution has no absolute significance; it allows the variation of the properties of the interphase with change of composition of the bulk phase to be predicted, insofar as these change the electrical properties of the

interphase. Now, (H^+) must have the dimensions of a volume concentration, whereas the distribution of hydrogen ions in the depth of the interphase is non-uniform. Hartley and Roe (9) calculate a differential value for (H^+) as a function of the charge of the interphase and the ionic composition of the bulk phase; this corresponds physically with the quantity of hydrogen ion per unit volume of an infinitely thin lamina infinitely near to a surface in which the charge is located. This definition of (H^+) is dimensionally correct and physically exact; it is a perfectly legitimate means of expressing the variation in interphase properties with those of the bulk phase.

Danielli (10) also calculates (H^+) by the much less legitimate device of supposing that there is a Donnan membrane parallel with the charged surface and distant $1/\kappa$ (the characteristic distance of the Debye-Hückel theory) from it; he assumes uniform concentrations on both sides of this membrane and Donnan equilibrium across it. He is fortunate that, for surfaces of small curvature, this treatment yields the same value of (H^+) as does Hartley and Roe's.

The objection to the use of the Debye-Hückel theory to calculate a value of (H^+) in the interphase is that it is not in accordance with the standard application of it to small ions. Hartley and Roe suggest that it should be applied to the calculation of the value of (H^+) at the surface of even small ions and that the value of K for such ions should be that in which there is no surface excess of hydrogen ions. But such a state is in practice unattainable and there seems to be no good reason for abandoning the traditional use of the Debye-Hückel theory for calculating activity coefficients relative to an approachable standard state.

3. *Activity coefficients.* The use of the activity coefficient term has the advantages that it is the traditional method of treating the variation of the properties of small ions and that it introduces no new difficulty over the definitions of K and (H^+), which have the same meanings and values as in the bulk phase. The activity coefficient expresses in a formal fashion differences in the mutual energies of ions, as measured or calculated, from their values in a defined and accessible standard state. The illegitimacy of the expression of the activity coefficient of a single ion is well known. The setting up of physical models which have a spurious air of reality, without giving any experimental or theoretical advantage, is avoided. Cannan (11) has made use of the calculation of activity coefficients in describing the titration curves of complex electrolytes as a function of the composition of the solution.

All these three involve the same application of the Debye-Hückel theory and differ only in the way in which the results are expressed. The choice is therefore not between principles but between modes of expression. The last is to be preferred. The term "pH" has been intentionally avoided in the discussion of interphases. It is now seen that "surface pH" can refer only to a surface excess or to a function of a rather unreal "concentration". By the proper use of activity coefficients its use can be avoided. Loose talk about the "pH of interphases" is to be condemned.

Finally, it should be remembered that only the electrical properties of interphases can at present be treated theoretically in a quantitative manner, and

then only in simple cases. The changes in degrees of dissociation of groups in the interphase with changes of composition of the bulk phase can be so far predicted, and are reflected in the changes of measurable properties of the interphase relative to the bulk phase. Agreement between the changes of several measurable quantities does not necessarily strengthen confidence that no factors other than the electrical are of importance. For example, the agreement between thermodynamic and electro-kinetic changes found by Danielli (10) serves only to show the consistency of the Debye-Hückel treatment as applied in these two fields, not the correctness of a predicted "surface pH".

CONCLUSIONS

It is concluded and recommended that:

1. Wherever the term "pH" is used in exact thermodynamic equations it should bear the single meaning "$-\log(H^+)$" and should always be written "pH_S".

2. Where "pH" is used as an empirical means of specifying the acid-base properties of solutions, derived from some particular means of measurement, it should be written without subscript. In giving its value, the method of measurement, its standardisation, and details of the composition of the solution (such as the kinds and concentrations of buffer and neutral salts) should also always be specified.

3. The use of the concept of "membrane potential" should be avoided.

4. The term "pH" should never be used with reference to interphases.

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A REVIEW OF PHYSIOLOGICAL AND PSYCHOLOGICAL STUDIES OF SEXUAL BEHAVIOR IN MAMMALS

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Purpose and Methods. As used in this article the term "sexual behavior" refers exclusively to the overt acts comprising heterosexual copulation, to those contiguous reactions commonly designated as "courtship" or "precoital play," and to a variety of non-copulatory sexual responses such as those involved in auto-erotic and homosexual activities.

The references and discussion which follow have been assembled and organized in an attempt to serve three purposes: (1) to bring together various neurological and endocrinological data concerning the strictly physiological aspects of sexual behavior; (2) to integrate with these relatively clear-cut results of laboratory investigation certain less definitive but equally important psychological findings reported by students of animal behavior, by practical animal breeders and by clinicians; and (3) to attempt to derive from this psycho-physiological potpourri a series of inter-species comparisons which may implement an evolutionary interpretation of human sexuality.

Merely to list and summarize the physiological experiments would have been a comparatively simple task, whereas the interpolation of non-physiological evidence has proven very difficult, and the result leaves much to be desired as far as logical organization is concerned. Nevertheless in preference to an annotated bibliography I have chosen to offer a complex and unavoidably incomplete survey of an important field of knowledge in the hope that presentation of the physiological and psychological data side by side will emphasize the essential unity of the phenomena dealt with by different disciplines, and with the expectation that the frequent lacunae revealed by this method may call attention to the urgent need for further research by investigators in many areas of science.

Importance of the Holistic Approach. Physiological experiments designed to identify the nervous pathways involved in a particular genital reflex, or to measure the importance of secretions from a single gland to the occurrence of copulatory reactions have contributed a great deal to our understanding of sexual behavior. It should be obvious, however, that the full significance of such findings becomes apparent only when they are viewed against the broader background of the total sexual pattern as it appears in the normal animal.[1]

Mating reactions are best interpreted as responses to internal and external stimuli,—and these responses are mediated by complex neuro-muscular mecha-

[1] It has been shown, for example, that decorticate female rats are capable of fertile copulation with the male (44), and this observation taken alone might be thought to signify that the loss of neo-cortex is without effect upon the female's sexual reactions; but subsequent investigation revealed that after destruction of the neo-pallium the mating pattern is modified so profoundly that males discriminate against operated individuals and will mate with them only when normal females are not available (45).

nisms whose functional capacity depends upon genetically-determined structure, upon concurrent activity in other nervous circuits, upon the composition and concentration of hormones present in the organism, and in varying degree upon the previous experience of the individual. None of these contributing factors operates in isolation, and the functions of one cannot be considered save in terms of its interrelations with all other variables involved.

FUNCTIONS OF THE NERVOUS SYSTEM IN SEXUAL BEHAVIOR. For purposes of analysis the rôle of the nervous system in sexual behavior may be considered as divisible into receptor and effector functions. In connection with both categories one must include the task of integrating separate units into a complete pattern. Thus, both the peripheral reception of separate stimuli and the central correlation of multi-sensory impulses belong under the same rubric; and motor functions are assumed to include not only the mediation of separate genital and postural reflexes, but the organization of these individual reactions into a unified pattern of response.

A. *Sensory Functions.* 1. *Evolutionary importance.* Identification of the sensory basis for sexual arousal is a matter of prime importance not only to the physiologist and the psychologist but to the student of evolution as well; and the concept of "sexual isolation" is one which systematists and geneticists find very useful in explaining the continued separation of closely related and inter-fertile sympatric species.

Sometimes referred to as "psychological isolation," this condition is defined as "absence of mating due to lack of mutual attraction" (98). "Sexual isolating mechanisms" are believed to include differences in behavior, in smells and in adornments which make males and females of different species less apt to find each other or less attractive and thus less willing to court and mate (99, 209).

Thus the problem of defining the stimuli responsible for sexual behavior is at the same time one of determining the basis for "species recognition" which is a governing force in evolutionary change.

2. *Inadequacy of simplified concepts.* Before one can appreciate the significance of experiments dealing with the functions of sensation in sexual behavior it is necessary to recognize the inadequacies of one particular line of thought which for many years tended to dominate research in this field and to obscure the true nature of the phenomena concerned. Over-simplified concepts of the neuro-physiological processes underlying sexual arousal, and naive interpretations of mating behavior as a sequence of concatenated reflexes early led to a search for *the stimulus* which set off the hypothesized chain reaction.

Presently available evidence permits the categorical statement that there is no single form of stimulation which can be regarded as the *sine qua non* for sexual arousal and copulatory reactions in male or female mammals (40). On the contrary, activation of several sensory systems normally contributes to the occurrence of the behavior in question and any single afferent pathway is dispensable provided the rest remain. From the psychological point of view it appears that the stimulus which initiates mating is not a single characteristic, but a pattern with certain characteristics of organization (187).

It is possible to go further and point out that even in the case of such restricted and incomplete segments of the total pattern as erection in the male or assumption of the copulatory crouch by the female the problem of sensory control is not a simple one; for almost every such reaction appears subject to alternative and supplementary forms of effective stimulation.

3. *Importance of individual differences.* It should be stated explicitly that investigation of the sensory control of sexual arousal involves problems of a higher order than those presented by the identification of stimuli adequate to elicit the separate muscular and glandular reactions involved in copulation. Definition of the stimuli evoking ejaculation is an important step toward the complete understanding of sexual activity; but exposition of the forms of stimulation responsible for pre-coital courtship and subsequent copulatory reactions is a much more complex affair which is likely to succeed only if approached with full recognition of the sources of variability capable of affecting the experimental results.

To illustrate,—male dogs and cats display erection in response to manipulation or electrical stimulation of the penis. This reaction can be evoked repeatedly and there seems to be little individual or temporal variability in the stimulus-response relationships involved. In contrast there are great differences between individual males or between the reactions of the same male at different times in respect to the ease and rapidity with which courtship and copulatory reactions can be induced.

Even when the conditions of external stimulation are held as nearly optimal and constant as possible the facility with which mating reactions are called forth differs markedly among male rats (4, 41), rabbits (196), guinea pigs (218), cats (reviewer's observation), sheep (211), pigs (144), rhesus monkeys (175), chimpanzees (55, 105, 326) and, I suspect, every other mammalian species. Individual differences in sexual responsiveness appear in male rats which have been reared in isolation (41), and are so extreme that a few obviously healthy and fertile males never attempt to mate with the receptive female (4). Variations in sexual excitability occur in boars despite a normal hormone balance (144), and wide individual differences are seen in male rats castrated at birth (50).

Differences in the ease with which initial arousal occurs are an important factor in any investigation of sensory function in sexual behavior, for they determine in part the quantity and quality of external stimulation necessary to evoke copulation. Although the majority of sexually-inexperienced male rats attempt to mate only when stimulated by a female in full estrus, a few highly excitable individuals which have been reared in isolation execute copulatory attempts when presented with non-receptive females or young males (41). Most male baboons actively court only those females in which the sex skin is swollen, but some males repeatedly mount non-estrous females (335); and in like fashion some male chimpanzees try to mate with any female at any stage of her sex cycle, while other males will copulate only at the height of the female's genital swelling and may even display a strong preference for individual females (105, 326). In general

it appears that, other factors being equal, "the specificity of the stimulus adequate to elicit mating responses varies inversely with the sexual excitability of the individual" (40).

Although presently available evidence would appear to suggest that the magnitude of individual differences in sexual responsiveness is much greater in male than in female mammals, there are several indications that females differ one from another in the ease with which copulatory reactions may be evoked. Some female rats in heat display lordosis each time they are mounted by the male, whereas other estrous females do not exhibit this reaction every time they are stimulated but do so in response to a constant and predictable proportion of the male's copulatory attempts (45). Similarly, ewes in full estrus show individual differences in willingness to stand for the ram and in readiness to take the initiative in courtship (211).

Individual differences in sexual excitability among male animals not only affect the initiation of copulatory behavior, but may be seen to influence the amount of stimulation necessary for ejaculation. Some male rats reach the peak of excitement essential to ejaculation after only two or three intromissions, whereas other males of the same strain do not attain this level of arousal until intromission has occurred fifteen or twenty times (35, 314). It is especially significant to note that in repeated sex tests the frequency of copulation in a given period and the number of intromissions preceding ejaculation are relatively constant for individual male rats as shown by the high reliability coefficients reported by different investigators (4, 31). Observations of copulatory behavior in the rhesus monkey have revealed that the number of mounts preceding intromission may vary from three to one hundred depending upon the "virility" of the individual male (75).

It seems probable that variations in sexual excitability are responsible in large measure for marked differences in the general character of the sexual approach shown by different males, particularly those of the higher primate species. Some male chimpanzees react to the female very abruptly, indulging in little or no foreplay and copulating vigorously or even violently, whereas other males practice a great deal of pre-coital stimulation, treat the female gently and copulate only after considerable preparation (55).

4. *Functions of non-contact stimulation.* a. *In the female.* The limited experimental evidence might lead one to believe that mating behavior of female mammals normally takes place without the intervention of visual, auditory or olfactory sensations; for removal of the eyes and the olfactory bulbs and destruction of the cochlea fails to abolish copulatory responses in the female cat (23) or rabbit (65). Actually, of course, these findings mean merely that when such drastically desensitized females are mounted by the male they respond to the resultant contact stimuli with appropriate postural adjustments facilitating intromission.

The complete sexual pattern of estrous females of most mammalian species includes active orientation to the distant male, and if the male is slow to respond

the female may initiate courtship. For example, the onset of estrus in the heifer is signallized by her tendency to seek out and stand beside the bull (1a), and female rats in heat display an increased drive to cross an electrified grid interposed between them and the male (313). If the male fox is not sufficiently aggresive the estrous vixen begins courtship play (108). Although the non-receptive female rhesus usually avoids contact with the male, when in heat she repeatedly approaches him, displaying a characteristic stance and stereotyped gestures (75). Female chimpanzees at the height of genital swelling may exhibit the sexual presentation and by various gestures and vocalizations invite the male to copulate (326).[2]

Reactions such as these obviously depend upon distance reception of one type or another, and although supporting experimental evidence is lacking it seems highly probable that the behavior described would be lacking in females which were blind, deaf and anosmic.

b. *In the male.* Although female mammals generally show an increased tendency to associate with males during the breeding period and may even instigate courtship when the masculine partner is slow to respond, it is commonly the male who plays the more aggressive and dominant rôle in the mating relationship. Even when the female begins the foreplay, initiative eventually must shift to the male if copulation and fertilization are to be accomplished, and it may be for this reason that distance receptors play a more fundamental part in the sexual functions of male than of female mammals.

The male animal's ability to detect the female's readiness to mate varies from species to species, from individual to individual, and even from time to time in the same individual. In the case of some sub-mammalian forms, such as certain amphibia, there is little indication that males can discriminate between receptive and non-receptive females, and sex recognition seems to be largely a matter of trial-and-error (228). Even male mammals which ordinarily are capable of discriminating between the estrous female and other animals may fail to respond selectively when highly aroused. Thus male rats (289) and guinea pigs (270) excited by recent contact with the receptive female often attempt to mate with other males or with diestrous females; and buck rabbits abruptly separated from the estrous doe mount and ejaculate in response to a dummy female (103) or even the hand of the experimenter (196). Under similar conditions male dogs mount males or the non-receptive bitch (129), and male rhesus monkeys may mount other males, sometimes with anal penetration (76).

Despite occasional absence of discrimination there is ample proof that prior to physical contact males of many mammalian species respond differentially to other males, non-receptive females and females in heat. Male rats in revolving cages become more active if cages containing estrous females are placed nearby

[2] In the majority of human cultures open sexual solicitation by unmarried females is socially forbidden; but in some primitive tribes which constitute exceptions to this rule the female's invitation takes the form of direct exposure of the genitals (122), a reaction strongly reminiscent of the sexual presentation shown by females of other anthropoid species and of many lower primates as well.

(45 cm. or less) (269).[3] The male chimpanzee plainly recognizes when the female in an adjacent cage is sexually receptive, as his prompt erection and invitational gestures amply convey. Observation suggests that in this case the effective sensory cues are the female's gross movements, gestures, facial expression, and the condition of her external genitalia (326).

Results of experimental studies suggest that in male lagomorphs and rodents several distance receptors probably contribute to sexual arousal and to the orientation of mating activity. Removal of the eyes or the olfactory bulbs does not eradicate copulatory behavior in sexually experienced male rabbits (65, 262, 290) or rats (41, 286, 287); but either operation performed prior to the acquisition of mating experience reduces the probability of copulation in male rats (41). The finding that blindness or anosmia tends to increase the proportion of rats which fail to copulate has been interpreted as evidence of lowered sexual responsiveness consequent to the reduced sensory intake (40).

The importance of olfactory stimulation to sexual activity of male animals has been greatly exaggerated by some workers. It has, for example, been claimed that male rats isolated for six months from the odor of females suffer testicular atrophy and complete loss of sex drive, and that such animals are restored to physiological normality when females are placed in nearby cages (278). Repetition of the original experiments with adequate controls and careful study both of behavior and histological condition of the gonads and accessories has shown that none of the reported changes take place in males isolated for eleven months (239). Similarly the arrested genital development and reproductive failure which is reported to follow removal of the olfactory bulbs in young male guinea pigs (199) probably is due, not to the loss of olfactory sensation, but to the severe brain infection which often follows this operation.

Laboratory findings concerning lower mammalian forms appear to minimize the functions of olfactory stimulation in the male's sexual arousal, whereas observational evidence has led commercial animal breeders and field naturalists to conclude that the odor of the female in heat is a potent force attracting and exciting the male. The validity of this conclusion has not yet been experimentally established but it seems probable that sensations of smell do contribute materially to the processes under consideration, although they are not, in all likelihood, the sole source of sexual stimulation in any species.

When they are in estrus the females of several mammalian species including the house cat (214), African lion (88), horse and cow (248) utter characteristic vocalizations, and it has been suggested that these "sex calls" stimulate males of the same species. Here again, although the supposition could be tested experimentally it has not been, and the only laboratory data available are those

[3] Although these findings originally were taken to indicate that the males sensed the presence of females in heat, the data are susceptible to an alternative interpretation. Female rats exhibit a striking increase in activity at the time of estrus, and it is possible that increase in the male's activity was simply a response to auditory and vibratory stimuli provided by the revolutions of the female's cage.

indicating that partial destruction of the cochlea does not eliminate mating in the male rat (286, 287) or rabbit (65).

Mating behavior survives combined elimination of visual and olfactory end-organs in the experienced male rabbit (65) and rat (286, 287); but copulatory reactions rarely appear in male rats which are rendered blind and anosmic before contact with the receptive female (41). The fact that the combination of blindness and anosmia depresses sexual responsiveness to a greater degree than does either type of sensory loss alone is taken as additional proof of the theory that both visual and olfactory stimuli normally contribute to sexual arousal (40).

5. *Functions of contact stimulation.* a. *Extra-genital stimulation in the female.* Various types of extra-genital contact elicit the copulatory posture and appear to increase sexual excitement in estrous female mammals. Some female rats in heat exhibit hopping, ear-vibration and lordosis when the back and sides are stroked or palpated lightly with the thumb and forefinger (16, 314). Stroking the rump of the estrous female guinea pig evokes opisthotonus and elevation of the perineum (329), and similar reactions may be elicited in the sexually receptive golden hamster by stroking or pressing the small of the back (reviewer's observation). If one presses heavily upon the back and sides of the sow in heat and simultaneously moves the tail to one side, the female responds by lifting the tail and hind quarters, presenting the genitalia, and grunting as in copulation (3). Receptive female cats can be induced to assume the mating position if the experimenter grips the loose skin of the animal's neck between his fingers and strokes or presses downward upon her back (23).

In each of the foregoing situations the inciting stimuli mimic those normally provided by the reactions of the sexually active male. Thus, prior to mounting the female, the male cat grips the skin of the back of her neck with his teeth, and the resulting stimulation is partially responsible for the female's assumption of the copulatory crouch,—a position essential to complete mating. A similar function should probably be referred to the comparable mating grip which is shown by males of several other species, including the short-tailed shrew (232), marten (204), mink (109) and bat (317). In some species such as the bat the male does not show penile erection until after gripping the female.

In the normal pattern of pre-coital play males of many mammalian species apply a variety of forms of tactual stimulation to the receptive female. In most species the male bites or nibbles at many parts of the female's body but animals with prehensile forelimbs may employ the hand and fingers as well as the mouth. The male monkey's manual grooming of the female increases in frequency when she is in heat (75), and involves "stimulation of most of the major receptor zones" (175).

Male animals of various species often bite or suck the female's ear before or during coition, and although there is no physiological evidence to prove that this form of stimulation is sexually exciting to the female, her subsequent responses often suggest that such is the case. In this connection it is significant to note that manipulation of the external ear produces contractions of the smooth muscles of the vagina in the estrous female cat (63).

The stimulatory activity of the sexually aroused male sometimes develops into active aggression with the result that the receptive female may suffer severe wounds. This is commonly observed in such widely separated forms as the marten (204) and the rhesus monkey (75).

Many of the pre-coital and coital activities characteristic of other animals are also present in human behavior, and the high frequency of such common elements suggests the existence of a basic pattern underlying the sexual activities of all mammalian species. For example, although no reliable evidence has been published to indicate the types of sexual stimulation most frequently employed in European cultures, it is well established that in many primitive tribes such as the Trobriand Islanders (201) and the Ainu and Toda of Eurasia (122), biting, scratching and hair pulling are common precursors and accompaniments of intercourse.

Despite the impressive degree of inter-species coincidence in many sexual responses it is obvious that specialization of morphological structures or nervous arrangements may give rise to particular forms of behavior which are restricted to the species so affected. It is well known, for instance, that in the human female the breast is a particularly sensitive erotic zone, and manual and oral stimulation of this area is a prominent element in the pre-copulatory pattern not only in European cultures but in other groups such as the Hopi of North America and the Lepcha of Eurasia (122). The "love magic" of certain Melanesian tribes involves surreptitious touching or caressing of the nipples of the woman whose favors are sought,—a custom based upon implicit recognition of the sexually-exciting powers of such stimulation (201). There is little evidence for this particular type of sexual stimulation in lower mammals, although one worker, observing that female rhesus monkeys in heat may manipulate and suck their own nipples, has interpreted this as auto-erotic (76).

b. *Extra-genital stimulation in the male.* Male rats continue to copulate despite surgical interference with cutaneous sensitivity of the entire ventral body surface (286, 287), and transection of the sensory nerves serving the snout and lips does not abolish mating activity in this species (41); but except for these reports there are very few data to indicate the importance of extra-genital sensations of touch and pressure to the occurrence of sexual arousal and coital behavior in male animals.

c. *Genital sensations in the female.* It was at one time a rather widely accepted view that sensory impulses from one or another part of the reproductive system are responsible for sexual arousal in female mammals; and one finds in the literature the statement that estrous changes within the vagina are, "the real internal stimuli for sex behavior in the female rat" (314), or that the "female hormones are psychologically important where they increase the local irritability of the sex organs, and thereby bring increased drive for further stimulation" (159a). A less extreme view is represented by the suggestion that sensations arising from direct vaginal or cervical stimulation are essential to and responsible for the receptive female's copulatory responses.

Several lines of evidence combine to indicate that neither of these theories is

sufficient to account for the behavioral phenomena under consideration. Normal estrous reactions occur in estrogen-treated female rats with congenital absence of ovaries, tubes, uterus and external vagina (48) and this would appear to negate the hypothesis that sensations from accessory sex structures are indispensable, inciting stimuli.

The belief that stimulation of the vagina and cervix is essential is equally untenable. In the first place, females of various species occasionally exhibit characteristic heat responses prior to any physical contact with a second animal. Highly receptive female rats may display hopping, ear-vibration and lordosis even though the male does not approach them (reviewer's observations), and some estrous cats crouch and tread spontaneously in the absence of the male (24). Secondly, as was pointed out in the preceding section, the copulatory adjustments of the estrous female are often elicited by various types of bodily contact which do not involve genital stimulation (e.g., crouching and treading may be evoked in the female cat by gripping the loose skin of the neck).

Finally, various experimental studies have shown that elimination of sensations from the genital region does not abolish mating behavior in the female. Removal of the uterus and vagina fails to eliminate copulation in the rat (11), and sexual reactions survive deafferentation of the entire genital region in the female rat (9), rabbit (65), and cat (21). Characteristic mating responses appear in female mice (247) and rats (48) despite congenital abnormality which includes absence of an external vagina.

Surgical removal of the tubes and uterus has even been reported to increase sexual responsiveness in approximately one-third of the women so operated (312), but this change may well be due at least in part to eradication of the fear of pregnancy.

Females of several species including the rabbit (66), cat (127), short-tailed shrew (232), mink and ferret (109) do not ovulate spontaneously, but usually do so only after copulation with the male. It has been assumed that in such cases mechanical stimulation of the vagina and cervix gives rise to nervous impulses which cause the hypophysis to release an "ovulation-inducing substance" which acts upon the ovary. It is, however, informative to note that when estrous female rabbits mount other females in masculine fashion ovulation is sometimes induced in the mounting individual, although under such conditions vaginal stimulation must certainly be minimal (158). Furthermore, female mink and ferrets in heat may ovulate after a prolonged struggle with the male despite the fact that mating is not accomplished and intromission does not occur (109). It would appear that in species which do not ovulate spontaneously ovulation is normally facilitated by the occurrence of sexual arousal and that intense excitement may call forth the ovarian response in total absence of primary genital contact.

If it is accepted that impulses from the genitals are not essential to the basic coital performance of female mammals it must be equally apparent that under normal conditions genital sensations provide one very important source of increased sexual excitement. In many species the male manipulates the female's

genitalia before coition; and among lower mammals such as the rat, guinea pig and golden hamster the male's oral investigations of the vaginal orifice often evoke overt responses on the part of the receptive female. The estrous hamster, for example, elevates the perineum (247b) and moves the hind quarters convulsively from side to side in response to the male's lingual exploration of the ano-genital region (reviewer's observations). When the male porcupine noses the vulva of the female in heat she backs toward him vigorously, pushing actively against the source of stimulation (265a). The male eastern skunk induces the receptive female to assume the copulatory pose by scratching at her vulva with his hind foot (315a).

Species with prehensile forelimbs usually employ manual as well as oral techniques of genital stimulation. The pre-copulatory play of rhesus monkeys involves mutual genital manipulation which "generates obvious excitement" (175). The male chimpanzee's manual and labial manipulations of the female's clitoris call forth erection and motility of this member, and female chimpanzees in heat have been observed to practice mutual cunnilinguis (55).[4]

Masturbation of the woman is common in the pre-coital play of various human tribes such as the Anunta of Oceana (122), and in certain sections of the Trobriand Islands both manual and oral forms of stimulation are characteristically employed (201). The effectiveness of such activity rests upon the innervation of the regions affected, and it is known that in the human female the clitoris and inner surface of the labia minora are richly supplied with sensory receptors for touch, although the vaginal entrance is relatively poor in sense endings of any type (53).

Evidence for the importance of genital sensations in feminine sexual behavior is not entirely inferential. Although rats surgically deprived of uterus and vagina are capable of mating behavior, in consecutive copulations such individuals typically display a decrease in responsiveness to the male which is probably traceable to absence of genital stimulation (11). Normal estrous females of this species are sometimes partially resistant at the beginning of a sex test but frequently display a marked increase in willingness to accept the male after one or two intromissions have occurred; and female cats which fail to crouch when gripped by the male may do so after the penis comes in contact with the vagina (25). Some female rats in heat exhibit lordosis when a pipette is inserted in the vagina (45), and comparable mechanical stimulation evokes crouching and treading in the receptive female cat (25).

During ejaculation the male rat deposits a copulatory plug within the vagina of the female, and the resultant stimulation causes a momentary relaxation of the cervix permitting passage of the sperm mass into the uterine cornua (57). The foregoing sequence of events is strongly suggestive of orgasmic function occurring in the female in response to internal genital stimulation.

d. *Genital sensations in the male.* Despite occasional statements to the con-

[4] Observations of this type are pertinent to an understanding of the biological basis for various human sex practices and cast considerable doubt upon *a priori* definitions of "normal" and "abnormal" forms of genital stimulation (28, 244).

trary (226) sensory impulses from the penis do not appear to be indispensable to sexual arousal because male cats seize the female, display erection and copulate vigorously despite surgical anesthetization of the entire genital region (255); and male rats continue to show sexual excitement after surgical procedures have rendered intromission impossible (50).[5]

Nevertheless it is obvious that genital sensations constitute an important element in the stimulus pattern responsible for complete sexual arousal and copulatory reactions in males. Female chimpanzees may induce erection in the male by handling the flaccid penis (55); and the male dog displays erection and ejaculation in response to genital manipulation (23). In the absence of normal genital stimulation overt sexual behavior may be profoundly modified. For example, adult male rats with infantile penes exhibit a high proportion of incomplete matings, relatively few intromissions and extremely rare ejaculatory responses; and similar behavior is seen in males with fully developed copulatory organs from which a segment of the penile bone has been removed (50).

The importance of direct genital stimulation to complete sexual performance in humans of either sex undoubtedly is subject to considerable individual variation; and there is in addition some indication of the existence of racial, or at least cultural, differences in this regard. Melanesian natives are reported to achieve orgasm only after protracted copulatory contact involving much more genital friction than is necessary for climax in white Europeans (201); and results of a current interview study indicate that male American negroes from low socio-educational strata are much slower than whites in attaining orgasm. However, negroes of high social status (as measured by education, etc.) are closely comparable to whites in terms of ejaculation time (176).

e. *Genital sensations as a potential source of copulatory movements during sleep in lower forms and erotic dreams in humans.* Genital reflexes sometimes occur in the apparent absence of any external stimulation. For example, full erection is sometimes seen in male bats during their hibernation (317) and in breeding season male short-tailed shrews often show erection during sleep.

In the case of the shrew vaso-dilation of the copulatory organ is sometimes accompanied by additional elements of the coital pattern as indicated in the following quotation. "These [erections] occur while the animal is lying asleep on its side or back. First, the penis becomes erect; then the animal stirs restlessly and there are twitching movements of the hind legs .... After several seconds a number of minor thrusts are made, followed by one vigorous, deep thrust which is accompanied by repeated extension of the hind limbs as in actual copulation" (232). This pattern may be repeated two or three times before the animal awakes and several such episodes can occur within half an hour. These observations suggest the interesting thesis that under such conditions sensory impulses originating in the erect penis set off a train of neuro-muscular events reflected in the execution of most of the major elements in the normal mating pattern.

[5] Equally unsatisfactory are theories designating sensory impulses from other parts of the reproductive system as initiating causes. Thus copulation continues in male rats after removal of the vas (12), the seminal vesicles (56), or even the testes providing androgen is administered (266).

The resemblance between such behavior in lower mammals and the nocturnal emissions common in a high percentage of humans[6] is obvious, and although crucial evidence is lacking it may be suggested that the erotic dreams which sometimes accompany genital activity during sleep are initiated or at least reinforced by sensory impulses from the erect penis or clitoris.

6. *Central nervous effects of peripheral stimulation.* Consideration of the observational and experimental evidence indicating that arousal and intensification of sexual excitement normally involves several types of sensory stimulation has led to theoretical analsyis of the more central neuro-physiological processes concerned (41). It has been suggested that effector mechanisms responsible for integration of the motor acts of courtship and coitus not only receive fibers from the several receptor systems, but may also be subject to facilitative impulses arising within a functionally related but structurally independent "central excitatory mechanism" (40). The *c.e.m.* is assumed to maintain the excitability of the executive centers by distant facilitation; and this part of the central nervous system is regarded as the most likely substrate for the effects of multisensory or repetitive peripheral stimulation.

Thus it seems probable that, by virtue of spatial summation, simultaneous stimulation of several sensory receptors may evoke a response within the *c.e.m.* in much the same fashion as the concurrent arrival of two subliminal impulses over different afferents elicits discharge of a reflex center. Furthermore, successive combination may occur within the *c.e.m.* as a result of successive applications of a sub-threshold stimulus to a single effector (128).

B. *Effector Functions.* As explained at an earlier point in this review, the effector or motor functions of the nervous system in sexual behavior are taken to include both the mediation of the separate responses involved in courtship and copulation and the integration of these individual reactions into a well-organized, biologically effective pattern. Most writers agree that the two functions probably are carried out by different nervous mechanisms (187, 213, 265, 331).

1. *Fundamental elements of the coital pattern.* The complete mating pattern is a complex affair including preliminary orientation to the partner, execution of postural adjustments appropriate to coition, and occurrence of the essential genital reflexes.

a. *Sub-primate species.* The basic coital reactions are approximately the same in all sub-primate species (247a). The female's fundamental copulatory response consists of flattening or depressing the back with consequent elevation and exposure of the perineum, and in those species where it is necessary the tail is moved laterally. Primary elements in the male's performance include mounting the female from the rear with the forelegs resting on her back or gripping her sides, execution of piston-like thrusts of the hind quarters and insertion of the erect penis. During coition most male rodents palpate the female's sides with the forelegs. In some species, such as the cat and dog intromission normally occurs but once, and is prolonged until ejaculation takes place. In other species the male may mount, achieve intromission and dismount several times before, on a final copulation, ejaculation occurs.

[6] Reported by 75 per cent of 291 adolescent boys (246).

From time to time there appear in the literature reports of apparent exceptions to this generalized pattern of copulation in lower mammals, and it is amusing to note the consistent anthropocentrism with which observers describe ventro-ventro mating in various species. None of the published accounts bears careful scrutiny, and inaccurate observation or incorrect identification of the behavior observed usually is sufficient to explain the error. For example, reports of ventro-ventro mating in the sea otter seem questionable in view of the fact that the animals under observation were a considerable distance away and were partially submerged at all times (223). Or again, in one study drawings purporting to represent ventro-ventro mating in the hamster are in actuality illustrations of fighting behavior (234). For obvious reasons it is often assumed that porcupines are incapable of mating in the manner characteristic of most quadrupeds, and in fact some naturalists have described the copulation of this species as occurring while male and female stand facing each other. However, careful observation of tame specimens reveals that although pre-copulatory courtship often includes some sparring or wrestling when the pair stand erect (265b), intromission is anatomically impossible in this position. When the actual mating takes place the male approaches the female from the rear, resting his forepaws upon the ventral surface of her tail (which is curved upward and over her back), and the female elevates her perineum to expose the genitalia (265a, 300). The european hedgehog copulates in essentially the same fashion (164a).

The statement that the fundamental responses involved in the copulation of lower mammals appear in relatively stereotyped form should be qualified by the admission that considerable variability is possible,[7] and under experimental conditions individual animals may show a surprising degree of adaptability in their coital reactions. Although they cannot mate in completely normal fashion bipedal male and female rats from which the front legs have been removed in infancy are capable of fertile copulation with normal individuals of the opposite sex (242).

b. *Primates.* The copulatory pattern common to most sub-human primates resembles in many respects that of the lower mammals, although differences in body form are of course reflected in behavior. In coition the receptive female rhesus monkey bends forward at the hips, lowering the head and shoulders and presenting the genitalia; while the male rests his hands upon the female's hips and grips her hind legs with his feet. Two to eight pelvic thrusts occur in a single intromission and several mountings usually are necessary before ejaculation occurs (75).

The copulatory pattern characteristic of the adult chimpanzee is closely similar to that of lower primates, but detailed descriptions of pre-puberal sex play in this anthropoid species include repeated observations of the occurrence of ventro-ventro coition. This variant of the pattern usually begins when the male and

[7] Under certain conditions the male may attempt to mount the female from almost any angle, and highly excited male rats aroused by previous copulations with an estrous female may clasp and palpate a non-receptive female even while she is lying on her back in a defensive position, a reaction which the naive observer might mistake for true copulation.

female are seated embracing each other in a face-to-face position. The female leans backward drawing the male over her, her legs encircling his back. The male's feet are flat on the floor, and his upper legs embrace the female's pelvis, hips and thighs. Pelvic movements follow and intromission occurs in some instances (55).[8]

2. *Effector mechanisms in the spinal cord.* a. *In the female.* Evidence to be reported immediately below concerning the spinal integration of genital reflexes in male animals makes it appear probable that the female's clitoral reactions are mediated by neural circuits in the cord. There is no direct experimental evidence to support this hypothesis but it would seem to be in harmony with the fact that these simple genital responses appear very early in the post-natal life of female anthropoids. Thus, erection of the clitoris occurs in the female chimpanzee within the first few days after birth (55), and is present as early in the female human infant (208). Certain clinical observations also suggest the possibility of "partial orgasm" in the infant human, for it is reported that manipulation of the turgescent clitoris is followed by "unmistakable relief from tension and restlessness" (208).

Despite occasional contradictory reports it is fairly well established that neural elements within the spinal cord are capable of supporting many of the basic responses which constitute the adult female's copulatory pattern. Although female guinea pigs in which the cord is sectioned at any point between T5 and L2 are reported to show no estrous behavior (94), the bitch exhibits normal estrous and mating despite complete lumbar section (136); and female cats with the cord transected at C1 display treading, opisthotonus and lateral deviation of the tail in response to stimulation of the perineum. Some investigators have reported that the spinal cat shows this behavior only during natural estrus or under the influence of injected estrogen, and these workers conclude that the responses in question are short-arc reflexes which in the intact animal are phasically integrated by higher centers (197, 198).

There is some dispute regarding the genuineness of the estrogenic effect in this instance, and other writers claim that chronic spinal cats exhibit no "estrous" reactions (24). There is no attempt to deny the appearance of the responses described above, but it is stated that lateral deviation of the tail is shown by males as well as females, that treading and opisthotonus may be elicited in the anestrous

[8] It is of general interest to compare coital performance in the ape with ethnological descriptions of the copulatory techniques employed in various human cultures. In a few tribes the position most commonly adopted during intercourse resembles closely that of the other anthropoids, the male approaching the stooping female from the rear (122). More wide spread is a variation of the ventro-ventro position comparable to the foregoing description of prepuberal copulation in the chimpanzee. For instance, copulation as practiced by all tribes among the Australian Aborigines of the North-West-Central Queensland district has been described as follows: "The female lies on her back on the ground, while the male . . . sits on his heels close in front: he now pulls her towards him and raising her buttocks drags them into the inner aspects of his own thighs, her legs clutching him around the flanks . . ." (256). This general pattern of coitus is said to be the common form in most primitive societies, whereas the ventro-ventro position employed in many European cultures is regarded by primitives as less effective and even "abnormal" (122).

female, and that since they are not dependent upon estrogen such reactions cannot be termed "estrual" (24).

At this point in our survey we need not be concerned with the presence or absence of hormonal effects and it is sufficient to note that treading, opisthotonus and tail deviation, which are components of the normal feminine coital pattern, survive in the spinal preparation.

Female cats decerebrated at the pontile level respond to mechanical stimulation of the vulva with collapse of extensor rigidity of the forelimbs, and the resemblance of the resulting posture to the sex crouch has suggested to some observers the existence of a primitive bulbo-spinal mechanism mediating this element in the female's copulatory pattern (23).

b. *In the male.* That certain elements of the male mammal's copulatory pattern can be mediated by spinal mechanisms is shown by the elicitation of sexual responses upon stimulation of the cord, and by the survival of such reactions after cord section.

Application of a low voltage current to the sacral region of the cord evokes erection and ejaculation in male rabbits and rats (101), cats (264) and dogs (52), and trauma attendant upon cord section elicits the same responses in male guinea pigs (172). In guinea pigs transection between T12 and L1 is followed within one to seven minutes by "rhythmic movements of the ano-genital region,"[9] erection and ejaculation (8). The common appearance of priapism in hanged criminals (128) is probably attributable to traumatic stimulation of similar spinal mechanisms.

Evidence for survival of certain elements in the masculine sexual pattern in chronic spinal animals is to be found in the reports of several investigators. The spinal male cat exhibits erection when placed in a prone position which brings the genitals into contact with the substratum (102). Following supra-lumbar transection male dogs show erection and ejaculation in response to genital manipulation (23), and these reactions can also be elicited in male humans surviving the same operation (24).

Sexual activities integrated within the cord are not limited to genital responses, for certain gross postural adjustments characteristic of copulation may also be mediated at this level. After lumbar section male dogs respond to genital manipulation with a series of reactions that have much in common with the normal copulatory pattern. These include bilateral extension at the knees, ankles and hip joints, depression of the tail and downward curving of the pelvic portions of the body (261). Masturbatory stimulation of spinal man evokes a composite response (of which of course the patient is quite unaware) which is so obviously similar to copulatory activity that it has been termed the "coital reflex" (251a).

Descriptions of the survival of isolated sexual responses in spinal preparations should not be allowed to obscure the fact that these reactions are disconnected fragments of a complete pattern, and that in the intact animal the functional

[9] Although not specifically described, these movements are suggestive of copulatory thrusts.

activity of the spinal mechanisms undoubtedly is subject to extensive modification by impulses from higher regions of the nervous system.[10]

3. *Effector mechanisms in the sympathetic system.* Complete abdominal sympathectomy does not prevent fertile mating in the female rabbit (65), rat (9) or cat (21); but sympathetic innervation appears to be heavily involved in at least one primary element of the male's copulatory pattern, namely, the ejaculatory response.

Male guinea pigs subjected to abdominal sympathectomy or to section of the hypogastric nerves respond to subsequent transection of the spinal cord with the display of erection, but ejaculation does not occur (8). In this same species electrical stimulation of the sympathetic pre- or post-ganglionic fibers serving the genital region evokes ejaculation without erection (8); and in the male cat stimulation of the internal pudendal nerves elicits the ejaculatory reflex (264).

Failure of ejaculation due to interference with the sympathetic supply to the genitalia produces marked abnormalities in the copulatory behavior of male animals. Guinea pigs suffering sympathetic denervation of the genitals copulate repeatedly but do not ejaculate (10); and after the same operation male rabbits mate vigorously, but the responses accompanying ejaculation (utterance of a characteristic cry and falling off the female) are lacking (306). In the rabbit inability to ejaculate is reflected in persistent copulatory acts which continue unabated until both the male and female are totally exhausted (8). In the case of the male rat abdominal sympathectomy eliminates ejaculation (306) but does not abolish copulation; and sympathectomized rats have been described as "infertile" (8) or "impotent" (172) although the latter term is of questionable applicability inasmuch as active copulation survives.

Male cats in which the lower two lumbar segments and all of the sacral cord have been removed seize the estrous female, exhibit erection and copulate normally. However, if the operation includes extirpation of the abdominal sympathetic chains or removal of the inferior mesenteric ganglia, penile erection does not occur although the male still grips the female and attempts to copulate (255).

4. *Effector mechanisms in the diencephalon.* a. *In the female.* Nervous mechanisms lying within the diencephalon contribute to integration of the separate responses which comprise the copulatory pattern of female rodents, lagomorphs and carnivores. Results of several operative experiments indicate that in the case of the female guinea pig and rat the most important neural circuits are to be found within a restricted region of the hypothalamus. Mating behavior persists in both species despite transection of the brain just anterior to the mammillary bodies, but is eliminated by section posterior to the mammillary bodies and anterior to the superior colliculus (94). According to other workers the

[10] Direct physiological evidence for functional interrelationships between spinal and supra-spinal mechanisms is seen in the report that penile erection is difficult to elicit in the decerebrate male cat (23). Furthermore, in the intact male dog erection or detumescence can be conditioned like any other reflex, and the appropriate genital response can subsequently be evoked by application of the conditioned stimulus, e.g., the sound of a bell (207).

guinea pig's receptive responses depend upon only the most ventral portions of the anterior hypothalamus, and the mesencephalic tegmentum or the region of the mammillary bodies is not involved (117).

Destruction of the caudal hypothalamus is reported to have no effect upon mating in the female cat, whereas extensive invasion of the anterior hypothalamus eliminates estrous behavior in some females and fails to do so in others (24). In this case no essential mechanism is indicated, but these results suggest that certain types of hypothalamic injury may reduce the female's tendency to display mating reactions.

Although lesions interrupting the optico-hypophyseal tract are reported to eliminate estrus and copulation in the female cat (117), the behavioral change probably reflects interference with secretory function of the pituitary (with consequent ovarian failure and disruption of gonadal hormone production) rather than destruction of any critical executive centers. Descriptions of amenorrhea and loss of libido following injury to the floor of the third ventricle in the human female (301) are perhaps susceptible to similar interpretation.

b. *In the male.* In view of the apparent importance of this brain region to the mating activities of female mammals it is unfortunate that few experiments have dealt with the effect of diencephalic injury upon sexual behavior in the male. The single report available states that damage to the medial half of the hypothalamus tends to "depress" sexual behavior in male rats, although the general area apparently includes no structure essential for the integration of the copulatory pattern (78).

It has been observed that injury to the floor of the third ventricle may abolish sexual desire and potency in the human male (301), and a study of thirty-three men with head injuries in which the diencephalon was the focus of damage revealed complete or partial loss of sexual desire in the majority of cases (285). However, evaluation of such reports is especially difficult in view of the possibility of direct or indirect interference with pituitary function, with resultant degeneration of the reproductive glands and consequent elimination of testicular hormone.

5. *Effector mechanisms in the forebrain.* a. *In female rodents, lagomorphs and carnivores.* Observations to the effect that copulatory responses may survive in female mammals despite complete transection of the brain at the level of the anterior hypothalamus indicate that more rostral parts of the brain are not essential to such reactions, and results of various experiments confirm this view.

Injury to or complete removal of the cerebral cortex, hippocampus, and the caudate-putamen complex does not abolish coital activity in the female guinea pig (94), rabbit (65), rat (92) or cat (22). There is in fact some indication that neo-cortical injury may increase the frequency of certain mating reactions. Completely decorticated female rats exhibit an increased tendency to assume the copulatory position, display ear-vibration more frequently and show a decrease in the frequency of the back-kicking response by which the intact female occasionally repulses the male (45). Bilateral temporal lobectomy in female rhesus monkeys is followed by increased willingness to receive the male and by heightened frequency of masturbation (177).

Evidence for the survival of certain estrous reactions in partially or completely decorticated females should not be taken to mean that the mating behavior of the intact animal occurs independently of activity within the neo-pallium, for it is clear that the cortex normally plays an important part in the mediation of feminine receptivity. One element in the female rat's mating pattern consists of a tendency to seek out the male and to orient her pre-copulatory heat responses toward him (313). The decorticate female of this species shows frequent estrous reactions but exhibits no tendency to direct such behavior toward the male. Furthermore, although all elements of the normal copulatory pattern may survive total loss of the neo-pallium, the timing or integration of the separate responses usually is disrupted (45).

b. *In male rodents and lagomorphs.* There are no published reports to indicate the effects of exclusively non-cortical forebrain injury upon mating activity in male animals, for all investigations have dealt with the results of decerebration or with the effects of lesions restricted to the neo-cortex.[11]

It is known that grossly normal copulatory reactions survive in male rabbits despite removal of all neo-cortical tissue (65), although no quantitative data have been presented to indicate possible changes in sexual responsiveness after this operation. Mating reactions are also reported to have been shown by four of eight decorticate male rats (92), but in an earlier publication I have questioned the validity of these conclusions on the basis of the author's failure to reconstruct cortical lesions (which were probably much smaller than estimated) and because no direct observations of mating behavior were conducted (31).

More systematic studies of pre- and post-operative sexual behavior in cortically injured male rats have revealed several significant facts. Lesions destroying no more than 20 per cent of the cerebral cortex do not eliminate mating behavior regardless of the region or regions involved (31). Such findings are in opposition to earlier proposals concerning the existence of a focalized "sex center" in the cortex (77).

Destruction of 20 to 50 per cent of the cortex may or may not eliminate copulatory behavior (184, 292). Individual differences are pronounced, but if lesion size is held constant within these limits, coital activity tends to survive in males which were sexually very vigorous before operation and to be eliminated in those animals which showed a low pre-operative sex drive (46). As the amount of neo-cortical destruction increases above approximately 20 per cent there occurs a progressive decrease in the proportion of males continuing to copulate; and when the extent of bilateral invasion exceeds 60 to 75 per cent of the total neo-pallial mass sexual reactions are eliminated in all cases (32).

Quantitative methods for measuring and describing mating activity in male rats yield results which emphasize the inadequacy of any attempt to interpret the behavioral effects of neural injury merely in terms of presence or absence of a particular response. For example, even in those males which continue to mate despite cortical injury, the tendency to display sexual reactions decreases pro-

[11] I have observed normal copulation in a few male rats suffering destruction of approximately one-fifth of the caudate-putamen complex without cortical injury, but no quantitative tests were conducted and the findings have not been published.

portionately with increase in lesion size. Thus, although some individuals may continue to copulate after loss of half of the neo-cortex they mate in only 15 per cent of the post-operative sex tests, whereas coition had occurred in 100 per cent of the tests given before operation (31).

The exact nature of the cortical contribution to sexual behavior in the male rat is not understood, but it seems safe to conclude that the neo-pallium is not essential to the control of the motor pattern involved, for when brain-operated individuals copulate the overt reactions are grossly normal (92). Studies of the effects of restricted cortical injury upon sensory capacities in rodents have yielded results which suggest that absence of sexual behavior in decorticate animals cannot be explained as the result of intereference with major sensory pathways or areas of representation (46).

The behavior of decorticated males placed with females in heat is characterized not by abortive attempts to copulate nor by any other sign of interference with the overt expression of sexual excitement, but by the absence of any indication of primary arousal. Neo-cortical injury appears to decrease sexual responsiveness without seriously affecting either the capacity for reception of stimuli or for execution of the motor acts of courtship and copulation.[12]

Many isolated masses of nerve cells in the central nervous system appear to be concerned with regulation of general levels of excitement and to contribute little if anything to the specific patterning of reactions (186). For example, studies of the function of the bulbo-spinal system in animal locomotion have led to the proposal that "one may look upon the medulla as a *Stimulations organ* which maintains the excitability of the spinal cord at a level which enables the latter to display its full locomotor activity when exposed to extraneous stimuli at a comparatively low level of intensity" (143).

In the case of the male rat it is apparent that nervous mechanisms lying below the neo-cortex are responsible for organization of the overt acts of courtship and copulation, but the reactivity of the executive circuits to external stimulation depends in part upon some function of the cerebral cortex.[13] The specific nature of the cortical influence is not known, but it probably rests upon well-known neuro-physiological phenomena such as that of "distant facilitation" (69).

Relations between the cortical mechanisms and lower nervous circuits involved in sexual reactions should be conceived as reciprocal rather than unilateral, for

[12] This reduction in reactivity is, of course, not restricted to the sexual field. On the contrary, it is a widespread effect which influences many types of behavior; and concepts of decreased "exploratory activity" (185), reduced "vigilance" (160), lowered "attention" (137), altered "affective regulation" (236) and increased "apathy" (114) reflect the general recognition of decreased responsiveness consequent to brain injury.

[13] As will be shown later the excitability of the executive circuits is also altered by gonadal hormones. Normal sexual responsiveness in the male depends not only upon neural impulses from the cerebral cortex but upon chemical sensitization by testicular hormone. In intact animals administration of large amounts of androgen may raise the reactivity of the copulatory mechanisms well above normal (34); and in partially decorticated cases mating responses can sometimes be revived by androgen treatment (31, 46). It appears that in the latter instance the hyper-normal hormone level exerts a compensatory effect, maintaining normal reactivity in the integrative mechanisms for sexual behavior despite reduction in the facilitative influences normally provided by the cortex.

impulses of diencephalic, mesencephalic or even bulbo-spinal origin probably are capable of modifying the sexual functions of the neo-pallium. It is in fact known that, in cats, stimulation of specific hypothalamic nuclei facilitates certain types of activity within the cortex, and it has been suggested that "initiation or accentuation of motor phenomena during emotional states may have a basis in hypothalamic-cortical facilitation" (224).

The data presented above indicate that sexual arousal and mating responses are to be considered as manifestations of an extremely complex pattern of neuro-physiological activity involving mediation of some response items by spinal centers, phasic integration of separate reactions by higher circuits located between the cord and cerebral hemispheres, and facilitative or inhibitory interaction between the foregoing mechanisms and the cerebral cortex.[14]

In male carnivores. It is usually accepted that the specificity of cortical influence upon sensory-motor functions in different species is correlated with the general level of development of the neo-pallium. In contrast to smooth-brained rodents, carnivores possess a convoluted and fairly well-differentiated cerebral cortex, and it is therefore not surprising to learn that male cats sustaining particular types of cortical injury show disturbances of sensory-motor co-ordination which are reflected in the occurrence of inaccurate and abortive mating reactions.

Coital responses are reported to have survived in six of seven male cats suffering bilateral removal of the frontal cortex in combination with all tissue anterior to this region; but sensory-motor abnormalities consequent to the operation resulted in a high incidence of disoriented reactions to the female (183). An increase in sex drive is said to have occurred in some of the brain-operated males, but it is impossible to assess the significance of this statement in the absence of supporting quantitative data (e.g., decreased latency or increased frequency of copulation, more frequent or rapid attainment of ejaculation, etc.).

In an experiment which has not yet been published Dr. Arthur Zitrin and I tested the mating activity of twenty male cats before and after destruction of various parts and amounts of the cerebral cortex. We found that normal copulation was possible after unilateral hemi-decortication, or bilateral removal of the frontal, temporal, parietal or occipital lobes. However, although they mated normally in some post-operative tests, at other times animals with such lesions exhibited disoriented or unco-ordinated sexual responses. For example, operated males sometimes approached and gripped the female from the side instead of the rear, and then displayed erection and pelvic thrusts although they were not mounted and the genitalia were not in contact with any portion of the female's body.

Cats subjected to unilateral hemi-decortication in combination with destruction of the contra-lateral frontal pole exhibited a strong sex drive as reflected in re-

[14] The concept of cortical function in sexual behavior presented here resembles in several ways interpretations advanced more than thirty years ago in an attempt to combat contemporaneous theories of a cerebral sexual center. At that time it was suggested that the rôle of the cortex in mating, as in most vegetative and visceral activities, is generalized rather than specific; although it was recognized that in higher forms the neo-pallium may play an important rôle in the associative learning which directs and coordinates specific sexual reactions (221).

peated attempts to copulate and in the frequent occurrence of erection; but these animals were capable of coition only when they were placed upon the receptive female. Hemi-decortication with destruction of the contra-lateral occipital pole eliminated responses to the distant female; but males sustaining lesions of this type were capable of normal orientation and copulatory reactions as soon as they came into physical contact with the estrous queen.

Cats in which all of the neo-cortex had been removed showed no interest in the receptive female and made no attempt to copulate even when placed upon the stimulus animal. Other workers have observed that decerebrate cats and dogs show no mating reactions (24).

In such cases it is difficult to determine the extent to which sexual failure is due to interference with primary sensory capacities consequent to removal of cortical projection areas. It is known that destruction of the striate area in dogs and cats does not abolish all visual function (131), and in the latter species this operation produces no marked defect in optical acuity as measured by nystagmus induction (271). Furthermore, dogs subjected to extirpation of the auditory cortex retain the ability to discriminate sounds (2), and the acuity of hearing is only slightly impaired (132). Some sound discrimination is present in cats after removal of the entire neo-pallium (304). Bilateral loss of parietal, temporal, frontal or occipital lobes does not appear to depress olfactory or gustatory functions in the dog (1).

In spite of this sort of evidence, which indicates partial survival of sensory capacities in feline and canine species after destruction of various cortical projection areas, it is beyond question that extensive neo-pallial injury produces marked reduction in sensitivity to external stimulation, and one is obligated to consider the possibility that absence of copulatory reactions in decorticate or decerebrate male cats and dogs is due solely to interference with exteroceptive function.

Until more data are collected it will be impossible to prove or disprove any such interpretation; but it should be noted that the sensory impairment consequent to bilateral destruction of occipital, temporal, parietal or frontal lobes does not prevent copulation in male cats. Furthermore, even the pronounced sensory-motor disturbance produced by unilateral hemi-decortication combined with removal of the remaining frontal pole fails to obviate sexual arousal and coital attempts. After complete decortication, however, males give no sign of sexual arousal and make no response to the receptive female. When these cats are placed upon the female in the mating position they show neither erection (which is reported to occur in the spinal cat) nor pelvic movements. In harmony with these observations are the reports of other workers to the effect that decerebrate male dogs, "show no interest in the rutting bitch" (138).

It seems clear that in the case of male carnivores the cortex makes a more specific contribution to sexual performance than it does in rodents. The question remains as to whether, in addition to particular sensory-motor functions, the carnivore cortex also exerts a general facilitative influence upon lower centers more intimately involved in the mediation of courtship and copulation. At

present all that can be said is that such an effect is quite possible; for the striate cortex is known to exert non-visual as well as visual effects (188), and studies of the primate brain have led to the conclusion that several cortical projection areas, "participate in a more general type of integration that is dissociated from their functions as sensory regions" (173).

d. *In male and female primates.* There are no reports dealing with the effects of extensive cortical injury upon sexual activity in male or female primates. In connection with investigation of the psychological changes accompanying brain injury in the rhesus monkey it was noted incidentally that males suffering bilateral temporal lobectomy exhibited a striking increase in sexual drive. The important behavioral alterations in males included priapism combined with a marked rise in manual and oral masturbation and in the frequency of homo- and hetero-sexual intercourse (177); and females with similar lesions are described as giving similar indications of hypernormal sexual responsiveness. The significance of this report is not immediately apparent, but it will be recalled that loss of the frontal lobes is said to have produced increase in the sexual responsiveness of male cats (183).

Existing knowledge regarding the extensive encephalization of various functions in the primate brain (164) renders it highly probable that at this level of the phyletic scale removal of sensory and motor projection areas would produce marked abnormalities in the mating pattern of both sexes and might abolish all responsiveness on the part of the male.

6. *Evolutionary trends.* Comparison of the effects of forebrain injury upon the reproductive life of fish (227, 229), amphibia (6), reptiles (97), birds (254) and mammals indicates that this most recently evolved part of the central nervous system has come to play an increasingly important rôle in the control of courtship and mating responses (42, 227). The most obvious type of change at ascending levels within the mammalian order lies in the growing influence of cortical areas of representation involved in sensory and motor activities Progressive encephalization of sensory-motor functions has naturally affected all complex types of behavior, and this process seems to carry with it certain secondary alterations which are of particular importance in connection with the response patterns under consideration here.

It appears that as the lower neural mechanisms mediating various discrete sexual reactions come to be more and more dependent upon activity within the neo-cortex, several associated changes occur. (1) The variety of external stimuli capable of evoking sexual responses tends to increase; (2) the overt patterns of sexual expression tend to become more variable; and (3) the direct importance of the gonadal hormones to sexual behavior tends to decrease. These generalizations, which are based upon scattered and fragmentary evidence, undoubtedly are subject to many exceptions, and may eventually prove to be only poor approximations of the facts; but at the present state of our knowledge they provide a useful frame of reference which should be helpful to an analysis of the behavioral and endocrinological data that follow.

C. *Behavioral Data Related to the Neuro-Physiological Evidence.* Having sur-

veyed the physiological evidence concerning neural mechanisms responsible for some aspects of courtship and mating we may now profitably turn to the consideration of a complementary body of data consisting chiefly of observational or descriptive accounts of sexual activity in different mammalian species. Some of the material presented below offers support for conclusions based upon neurophysiological experiments. In other instances the behavioral evidence extends beyond results established by physiological techniques and points the way toward potentially fruitful laboratory studies.

1. *Relation between sexual behavior and non-sexual emotions.* Little is known concerning the neural basis for emotions in general, but observations of behavior strongly suggest a close functional relationship between the mechanisms for sexual behavior and other nervous structures which are activated during various sorts of intense emotional arousal. It is particularly evident that sexual responses may appear in non-sexual environmental settings which evoke strong emotions of different types; and conversely, stimuli which ordinarily elicit courtship and copulation may under certain conditions call forth vigorous non-sexual reactions indicative of high excitement.

That sexual mechanisms may be activated by non-sexual stimulation is shown by the fact that male dogs sometimes display erection and ejaculation in the presence of fear-inducing stimuli (129), and that the same responses frequently occur in male chimpanzees subjected to various types of excitement such as that engendered by presentation of food, separation from companions, or disciplinary contact with the trainer (55). Directly comparable evidence is available in the case of humans, for painful stimuli may evoke genital reflexes in young children (171), and pre-adolescent boys experience erection when frightened, as well as in other exciting but non-sexual situations (246). Sexual presentation is sometimes exhibited by both female and male rhesus monkeys in response to "generalized, non-sexual excitement" (75).

The sexual reactions which appear in conjunction with intense emotion are not limited to fragmentary, genital reflexes. On the contrary active sexual behavior may occur in such situations. For example, immature chimpanzees occasionally masturbate during a fit of anger (178), and cebus monkeys as well as apes sometimes indulge in manual or oral genital manipulation when confronted with a difficult learning problem (129). Similarly it is reported that school children often resort to genital play under the stressful influence of classroom examinations (171, 172). In human adults extreme frustration may lead not only to auto-genital activity but to complete hetero-sexual intercourse (260).

A state of generalized excitement seems in some cases to facilitate the occurrence and manifestation of sexual arousal. Female rats which have escaped from their cage and been recaught sometimes exhibit an increase in sexual excitability (16); and some males of this species which have become temporarily sluggish can be aroused to renewed copulatory activity if they are batted sharply about the cage by the experimenter (40). In some instances male rats which fail to initiate coital activity in response to a given estrous female may do so when a new stimulus animal is introduced, even though the second female is no more

receptive than the first (298). In this case it seems probable that the disturbance created by changing females is responsible for the male's arousal; an interpretation which gains support from the observation that the same result may be obtained by removing the original female and immediately re-introducing her into the testing cage (34).

Male rats which are regularly subjected to an electric shock just before and during the moment that a receptive female is placed in the cage react in subsequent tests by mounting the female the moment she is presented, and "copulating violently, almost frantically, *during the shock*" (314). This reaction is the opposite of that obtained if the shock is started when the copulation is in progress, or just after it is terminated. In the latter cases punishment inhibits sexual activity in following tests.

Male and female primates are known to show sudden increases in mating activity in response to exciting but non-sexual changes in the environment; and in some instances the change may be nothing more than the abrupt appearance of a human observer (55, 175). It is quite possible that the stimulating effect of non-sexual excitement is responsible for the discriminatory behavior shown by males of various species toward new or strange females. In free-ranging rhesus monkeys the stimulus value of a new female is greater than that of a female with which the male has been associated for some time, even though the latter animal may be fully receptive (75, 76). The result is that the male displays an increase in copulatory behavior when a new female becomes available. Human parallels are too obvious to deserve comment.

A high degree of sexual arousal often produces non-sexual manifestations of excitement, and this is particularly common when normal coital adjustments are blocked. For example, male rats with under-developed penes execute repeated attempts to copulate with the receptive female, but in the absence of intromission ejaculation is rare. When such animals become highly excited as a result of a series of incomplete copulations the frequency of attacks upon the female is much higher than in normal matings (50); and this increased aggression seems to be related to the occurrence of intense sexual arousal combined with the failure of ejaculation and orgasm. Female rats which are extremely receptive often launch vicious attacks upon males which persist in investigating and mounting but fail to copulate and achieve intromission.

The literature contains one report of an inexperienced male macaque which became intensely excited as a result of his inability to achieve intromission even though the female was highly receptive and attempted to guide the penis manually. After several unsuccessful attempts at coition the male left the female and began to bite his feet and legs, inflicting severe wounds. Thereafter the mere appearance of the female tended to throw this male into a frenzy of self-mutilation (310).

2. *Inter-sexual differences in sub-primate species.* Behavioral evidence which correlates with the results of certain physiological investigations is found in a list of differences between the sexual behavior of males and females of several lower mammalian species.

a. *Effects of non-sexual stimuli upon sexual arousal.* Among lower mammals extraneous, non-sexual stimuli have a tendency to inhibit sexual arousal in the male. Males of many species are inattentive to receptive females and slow to copulate in surroundings that are novel and strange; whereas under the same circumstances females usually mate without hesitation. This inter-sexual difference is recognized by commercial breeders (5) and on mink ranches, for example, it is customary to take the estrous female to the male's living quarters for service; for when the reverse procedure is practiced the male, "wastes time exploring the cage, etc." (179).

The absence of sexual arousal in a strange environment may be due to fear, but more frequently it appears that the male is merely distracted by non-sexual stimuli, a situation which occurs less commonly in the female. Thus although captive female coyotes permit copulation by male dogs, the reciprocal cross is difficult to bring about because the male coyote is easily upset by the artificial conditions of caging, etc. (95).

The sexually inhibiting effects exerted by a strange environment may be dissipated gradually as the male becomes accustomed to his new surroundings, and some individuals which fail to mate at the first contact succeed in doing so after they have been put with a receptive female in the same cage several days in succession. In repeated tests the proportion of male rats exhibiting coital reactions tends to increase (36); a result which is not typical of females and which presumably reflects individual variance in the readiness with which different males adapt to the testing situation.

In other cases environmental interference is promptly and completely eliminated as the result of one successful copulation. Regardless of the duration of their residence in the laboratory most male cats do not copulate when they are first taken to the testing room and placed with a receptive queen, and this refractory behavior tends to continue indefinitely until coition is once achieved. In some instances it is necessary to manipulate the experimental situation in order to induce the initial mating; but once this has taken place the male thenceforth displays spontaneous courtship and copulation in all subsequent periods (334). Estrous female cats, in contrast, mate readily during the first test under laboratory conditions.[15]

In some species the male is hesitant to mate with a strange female even though she is fully receptive, but comparable discrimination is not evidenced by the female. For example, the receptive female porcupine accepts any sexually aggressive male upon first contact, whereas males will not attempt coition with

[15] The observation that females are less likely than males to be distracted by non-sexual environmental stimuli finds its counterpart in the fact that females of several lower mammalian species are fully capable of attending simultaneously to sexual and non-sexual stimuli; whereas the male gives no indication of this ability. The estrous bitch accepts food even during coition, while the male is capricious about eating in the presence of a receptive female and most males refuse food entirely during copulation (129). I have seen female cats *in copulo* conduct extensive olfactory investigation of a mouse hole in the board floor of the testing room, although such a division of activity has never been observed in the case of the male.

any female until she has been kept in their cage for several days (265a). Males of various domesticated species sometimes refuse to serve certain types of females. A stallion which has mated exclusively with dark mares may show no inclination to mount a white one; and jacks which have been allowed to serve jennets are likely to refuse copulation with mares (206a).

The converse of environmental inhibition of sexual responsiveness can be seen in the behavior of males of several lower mammalian species. When a male has repeatedly received receptive females in a given external situation, the environmental setting tends to acquire sexually-exciting qualities with the result that coital reactions may be elicited by any one of a wide variety of stimulus animals offered in that setting. Although sexually-inexperienced male rats usually attempt to copulate only when given a female rat in estrus (41), many males which have copulated with receptive females in a particular testing cage will subsequently attempt to mate with males or non-receptive females (30, 174, 286), or even with females of a foreign species (41) when such animals are encountered in the original testing situation. Male rabbits accustomed to receiving estrous does in the living cage will, "mount cats, kittens, guinea pigs, and even dead or inanimate objects" offered in a similar fashion (65).

The sexual responsiveness of male mammals may be depressed in an environmental setting associated with conflict or pain. Neurotic male dogs are slow to mate with estrous females presented in the experimental room where the neurosis was induced, although in the paddock copulation may occur promptly (129).[16] Lasting inhibition of the male's sexual responsiveness sometimes results if arousal is attended by punishment. Male rats subjected to electric shock during or immediately after copulation with the female usually fail to mate in subsequent tests (314). Male marten which are scratched or cut by the female during mating are apt to show little interest in receptive females presented on succeeding days (204).

Experiences encountered during the first complete sexual contact exert a particularly potent effect upon subsequent responsiveness. In training young male foxes for service, breeders take care to select females that are gentle and in full heat in order that the male shall not be attacked or frightened and thus spoiled for future use as a sire; but such precautions are regarded as superfluous in the case of an experienced stud male (108). If a fight occurs during initial matings the young male mink is unlikely to develop sufficient aggressiveness toward the female; whereas after a few successful copulations, "he will have acquired confidence and his future as a breeder is assured" (179).

The facts that extraneous stimuli tend to interfere with the male's reactivity to the receptive female, and that previous experience may alter the male's susceptibility to sexual arousal appear to be closely related to the observation

[16] Evidence of this type may bear a significant relationship to clinical observations suggesting that conflict, anger or fear are capable of suppressing sexual tendencies in the human (74); that the majority of patients suffering "anxiety attacks" complain of sexual difficulties (129); and that interference with normal sexual function is a common symptom in various psychoses, particularly paranoia (306).

that the cerebral cortex exerts a profound effect upon copulatory behavior in the male but is less important in the coital adjustments of the female. In the case of the male a profusion of non-sexual stimuli may evoke within the cortex a series of activities incompatible with those essential to sexual responsiveness, with the result that the effector mechanisms for courtship and copulation receive no facilitative impulses from higher centers. Conversely, stimuli which originally possess little or no effect upon sex responses may, by a process of cortical conditioning, come to exert pronounced effects upon sexual mechanisms.

b. *Pre-puberal sexual activities.* In many sub-primate species there is a marked inter-sexual difference in the age at which recognizable copulatory reactions appear. Although female rats do not exhibit any part of the adult feminine coital pattern prior to the first complete ovarian cycle (which usually occurs at 45 to 50 days post-partum), males of this species mount and palpate other rats and may show pelvic thrusts as early as twenty-one days after birth (43). Comparable pre-puberal sexual responses are shown by male guinea pigs (193), hamsters (62), marten (204), cattle (169) and lions (88); but in none of these forms does the pre-pubescent female display the complementary feminine reactions.

These extreme differences probably are not due exclusively to neural factors, but are related in part to differential rates of development within the secretory portions of the male and female gonad. Thus the interstitial tissue of the testis matures earlier than its ovarian counterpart (27, 311), and produces hormone long before the ovary begins to elaborate and release its endocrine products (27, 169, 231). It seems likely, however, that the relatively early appearance of masculine sexual performance and the delayed onset of feminine receptivity is to be understood as depending upon central nervous differences as well as hormonal variation; for it has been shown that adult male rats which were castrated on the day of birth exhibit sexual responses that are identical to those characteristic of the intact, immature male (50).

3. *Sexual differences and similarities in primates.* Male and female monkeys, apes and humans do not exhibit the same inter-sexual differences as have been described for lower mammals, but certain types of variation which are apparent suggest that at these higher evolutionary levels the nervous elements involved in sexual arousal and coital performance are not identical in the two sexes.

a. *Pre-puberal sexual activities.* Both male and female primates display sexual responses during early life. Penile erection is present in the macaque soon after birth, and by the seventeenth post-natal day males repeatedly rub the glans against objects in the environment. Rhythmic sex patterns become a regular habit during the first year, and male infants use rubber playthings "in a sexual fashion" (166). The female rhesus shows sexual presentation as early as six months after birth. Infant chimpanzees of both sexes indulge in frequent and highly variable sex play which ranges from manual and oral masturbation to heterosexual copulation with intromission and pelvic thrusts (55).

In view of the common occurrence of pre-puberal sexual activities in every primate species which has been investigated it is not surprising that sex interests

are detectable in very young children of all cultures (122). In some social settings infantile sexual tendencies may not become well patterned until puberty (139), but social taboos against overt sexual relationships do not completely suppress such activity (245, 263).

From the evolutionary point of view it is especially significant that in cultures which permit free and unrestricted sexual expression, the common patterns of pre-puberal play bear close resemblance to those observed in the immature chimpanzee, including genital manipulation, oral contact and copulatory attempts with intromission and pelvic thrusts (201).

b. *Sex differences in adulthood.* Published accounts of sexual behavior in primates do not contain as many indications of inter-sexual difference as were cited above in connection with sub-primate species, but studies of reproduction in the chimpanzee indicate that certain important male-female variations do exist.

Adult male chimpanzees lacking experience in heterosexual relations often are unable to effect complete union on first contact with the receptive female. Sexual arousal appears to occur normally, for erection takes place promptly and the male usually attempts to cover the female. In most cases, however, the pattern goes no farther than this, and intromission and ejaculation are not achieved. In subsequent matings the copulatory pattern is gradually perfected and eventually sexual competence is achieved as a result of practice and learning (326).

The female chimpanzee lacking any mating experience is obviously better prepared for copulatory behavior than is the inexperienced male (55). When inexperienced females are caged with experienced consorts mating is carried out without undue difficulty, and even when the partner is a sexually naive male, the female's responses are adequate and may even include manual attempts to direct the penis into the vagina (326).

It is impossible to assess the importance of training and experience to sexual performance in the human. In the first place too little is known concerning the amount and diversity of sexual experience gained before reproductive maturity by members of either sex within our own culture. It seems fairly certain that the overt pre-marital sexual experience of the average male far exceeds that of most females (176); but the breadth of vicarious experience made possible by language would appear to obviate total naiveté in any individual.

The original data have been subject to a great deal of just criticism, but it may be worth while to point out that descriptions of "feral" man indicate a very low sex drive rather than an intense and undisciplined libido. The adult males Tomko of Zips and Kaspar Hauser are reported to have shown no interest whatsoever in sexual matters; and careful consideration of similar cases has led one reviewer to conclude that as far as humans are concerned, "the social channeling of sex is much more necessary for its full expression than might be thought" (333).

4. *Bisexual mating reactions.* Experimentalists ordinarily think of masculine sexual behavior as appearing in male animals, and feminine activity in females; but there are numerous observations to prove that normal, untreated female

mammals are capable of exhibiting nearly all elements of the masculine copulatory pattern, and that sexually active males occasionally display feminine coital responses. Animals showing mating activities typical of the opposite sex also execute the copulatory pattern of their own sex with normal frequency and effectiveness, and these facts must be taken into consideration in any analysis or interpretation of physiological mechanisms responsible for courtship and coition.

a. *Incidence and characteristics.* The display of male-like mounting with pelvic thrusts by normal females has been described in the case of the rat (29, 36, 51), guinea pig (331), rabbit (158), golden hamster (reviewer's observation), porcupine (265a), short-tailed shrew (232), marten (204), dog and cat (reviewer's observation), sow (3), cow (327), rhesus monkey (76, 149), and chimpanzee (55, 325). Records of the appearance of feminine sexual behavior in male mammals are less common, but estrous reactions have been observed in male rats (29, 47, 49, 289), guinea pigs (60), golden hamsters (reviewer's observation), rhesus monkeys (75, 149), and chimpanzees (55).

It is noteworthy that male rats which exhibit feminine sexual reactions invariably prove to be unusually vigorous copulators when placed with receptive females (29, 47, 289). They initiate coition with very little delay, execute few incomplete copulations and reach the point of ejaculation much sooner than most animals of the same strain. Furthermore, such rats are most likely to display female behavior at times when they are highly aroused as a result of previous contact with estrous females. It has been my experience that the most reliable method of eliciting the feminine mating pattern is to allow the male several copulations with a receptive female, to remove the female before the male can ejaculate, and to introduce a second male who will mount and palpate the bisexual individual. If the experimental animal is not sexually aroused, or if he has just ejaculated, it is difficult if not impossible to evoke feminine responses.

The ear-vibration, which is an integral part of the female rat's sexual pattern, may be executed during copulation by male rats that are highly aroused but incapable of ejaculation (50). The males which have been observed to show this reaction were individuals castrated at birth and injected with large amounts of androgen in adulthood. As a result of very early castration the penes were very small and did not permit intromission at normal frequency; but androgen treatment resulted in a high level of sexual excitability, and the experimental animals executed numerous copulatory attempts when placed with females in heat. Although the males gave many signs of being intensely excited, the infrequency of intromission prevented ejaculation; and under such conditions some individuals repeatedly displayed ear vibrations while they were mounting and palpating the female.

The foregoing observations suggest that the neuro-muscular mechanisms mediating feminine sexual reactions in the male are most likely to be activated when a state of pronounced sexual excitement exists, and when execution of the complete masculine pattern is prevented. In addition, of course, application of the appropriate pattern of external stimulation is essential if the entire sequence of feminine responses is to be elicited.

In connection with the question of external stimulation it should be observed that the masculine mating pattern is called forth in females by the same stimuli which evoke it in males, while the feminine responses of males are elicited by those external events which normally initiate these reactions in the female. Thus, female rats exhibit masculine mating behavior most frequently and intensely when they are confronted with other females which are highly receptive (51); and males of this species show feminine reactions when they are mounted and palpated by other males (47).

In considering these facts one becomes aware of the possiblity of dealing with courtship and copulatory behavior in terms of stimulus-response relationships which are relatively constant in all individuals regardless of genetic sex; and it is apparent that the neuro-muscular mechanisms responsible for many such relationships are present in both male and female mammals. In either sex the application of pressure to the dorso-lumbar region tends to elicit lordosis and opisthotonus; and in either sex the multi-sensory pattern of stimulation provided by the receptive female tends to evoke pursuit, mounting and palpation with pelvic thrusts.[17]

b. *Limitations.* It would be a mistake to minimize the limitations of potential bisexuality in mating behavior. Briefly stated these are three in number: (1) limitations imposed by differences in the ovarian and testicular hormones, (2) limitations imposed by genetic differences in the thresholds of responsiveness within the neural mechanisms for masculine and feminine behavior in the two sexes, and (3) limitations imposed by differences in morphological structure, particularly that of the genitalia.

As will be explained at a later point in this review, sensitivity to external stimulation within the neuro-motor circuits mediating masculine sexual responses is greatly increased by testicular hormone, while mechanisms for feminine responses are rendered sensitive by ovarian secretions. Therefore the masculine mechanisms in the genetic female are relatively insensitive because of the absence of the appropriate hormonal facilitation, and a similar situation obtains for the feminine mechanisms in the male.

Even in the absence of any gonadal hormones there is a difference in the ease with which masculine and feminine reactions can be elicited in male and female mammals. For example, the male rat castrated on the day of birth (50), and the male guinea pig subjected to similar operation long before puberty (275) are known to display rudimentary masculine sexual reactions when placed with the receptive females during adulthood; but such animals do not exhibit feminine copulatory behavior when mounted by other males. Thus it appears that in the genetic male the threshold of responsiveness in the neural circuits for mascu-

[17] The suggestion that the genetically-organized neuro-muscular system is, within limits, potentially bisexual, carries no implication of antagonism between the feminine and masculine mechanisms, and should not be confused with such nonsensical formulations as the following: "Thus one must assume that the cerebrum contains male and female centers whose antagonistic action and relative strength determine the individual's sex behavior. Homosexuality results from the victory of the wrong center" (244).

line coital performance is inherently lower than the threshold in the mechanisms for feminine behavior. Whether or not the inverse situation obtains in the female is not known, but a quantitatively similar differential may be assumed to exist, although it seems likely that the masculine circuits in the genetic female are more easily stimulated than are the feminine mechanisms in the male (51).

When a spayed female rodent is injected with androgen, and the neuro-muscular mechanisms associated with masculine sexual behavior are rendered highly sensitive to exteroceptive stimulation, the resulting behavior is less complete than that of the normal male. The difference appears to derive at least in part from the absence of masculine genitalia. Although she mounts other females in the same manner as a male, and executes numerous copulatory thrusts, the androgenized female executes relatively few complete copulations and does not show the ejaculatory pattern (15). In fact her behavior resembles closely that of adult males from which a portion of the penile bone has been removed (50). These observations make it possible to assume that the incompleteness of the pattern is in both instances referable to lack of intromission with consequent failure of one important source of sexual stimulation which operates to produce intense excitement in the normal male.

5. *Behavior involving auto-genital stimulation.* a. *Incidence and characteristics.* Under certain conditions male and female mammals of many species manipulate their own external genitalia. In some animals auto-genital stimulation occurs in close conjunction with copulatory behavior, under the influence of sexual excitement generated by previous contact with the opposite sex. Members of other species exhibit similar responses in isolation, and their behavior indicates that the resulting sensations induce definite erotic effects.

Although there have been no experimental attempts to determine the physiological mechanisms involved, the widespread occurrence of auto-genital manipulative reactions suggests that this type of behavior may be a fundamental element in the basic mammalian sexual pattern, and as such it deserves attention in the present review.

It is reported that sexually excited male porcupines manipulate the genitalia with the forepaws and often walk about on three legs, straddling a long stick which is held in one front paw and extends backward between the hind legs, coming into intimate contact with the penis (265a).

Licking and manipulation of the penis constitute integral parts of the coital pattern in many rodents, including the rat (286), golden hamster (247b), and short-tailed shrew (232). In the last-named species post-copulatory penis manipulation is thought to be essential to fertile mating, for after each mount regardless of the occurrence of intromission the male must return the penis to its sheath before he is capable of pursuing the female (232).

Ejaculation has not been observed in connection with auto-genital manipulation by male rodents and it is not at all certain that such activity is sexually stimulating, but there is some evidence to suggest this may be the case. According to some experimenters the male rat's penis licking often is accompanied by distinct pelvic movements similar to those occurring during copulation (286);

and males of this species in which overt copulation has been inhibited by electric shock respond to the presence of the estrous female with a pronounced increase in the frequency and duration of oral manipulation of the phallus (314).

Females of lower mammalian species characteristically nibble and lick the vaginal orifice after each copulation or series of copulations, and this response forms a particularly prominent element in the post-copulatory "after reactions" shown by female cats. The female porcupine in heat may seize and straddle small sticks, supporting one end with a forepaw and riding the stick about the cage in such a manner as to stimulate the external genitalia (265b).

Caged male rhesus (177) and cebus (129) monkeys often masturbate to the point of orgasm, and such behavior has sometimes been interpreted as an "abnormal" response induced by artificial conditions of sexual deprivation (149). This point of view appears to reflect moralistic conviction rather than accurate observation, for masturbation with ejaculation occurs in free-ranging, socially dominant male macaques which have free access to receptive females (76). Adult male chimpanzees frequently stimulate ejaculation by manual or oral masturbation (276), and immature males of this species masturbate several years before ejaculation is possible (55).

Auto-genital stimulation is not peculiar to male primates, for it occurs in the female rhesus (177) and in both infantile and adult chimpanzees (55) and gorillas (323). The female ape may masturbate with the fingers or with foreign objects such as fruit, pebbles, leaves, or projecting corners of boxes.

In humans as in other primates auto-genital manipulation begins long before puberty and occurs in a high proportion of the population. According to one authority, "masturbation with partial orgasm may begin in the first year of life and continue irregularly thereafter in both sexes" (208). Other observers state that grasping and manipulation of the penis are frequent by the third year in the human male. although genital stimulation is said to occur less often in the female (190).

Regardless of the exact age of its initial appearance (which must be subject to considerable individual difference) there is no doubt concerning the very high frequency of masturbatory behavior in reproductively immature humans, particularly males. In one series of interviews 90 per cent of 291 boys reported the practice of masturbation beginning before or soon after the onset of adolescence (246). That activity of this character is not limited to members of European cultures is amply demonstrated by reports of its widespread occurrence among primitive tribes (122).

b. *Establishment of masturbatory habits in the human.* In view of the common tendency to regard human masturbation as an "abnormal" or "substitute" response it may be worth while to point out one course of events by which deep-rooted habits of genital manipulation may be established during infancy or early childhood.

It is well known that in most if not all primates genital reflexes appear soon after birth. In the macaque monkey penile erection is seen during the second post-natal week (166), and penile and clitoral tumescence occur in chimpanzees

at birth (55). Male and female human infants exhibit turgescence of the penis or clitoris at birth, and in the case of males three to twenty weeks of age the average frequency of erection varies from four to thirty-five within a 24-hour period (148). The occurrence of a definite response to masturbation in human infants is indicated by the report that manipulation of the erect penis or clitoris is followed by "unmistakable relief from tension or restlessness" (208). Although the limited neuro-muscular capacities of very young infants would not permit prolonged auto-genital stimulation, it is known that grasping and handling of the phallic organs occur frequently by the third year (190).

To these data concerning genital activity must be added the fact that conditioned reflexes can be established in very young infants. For example, if a buzzer is always sounded just before presentation of the breast or nursing bottle, babies less than one week old react to the auditory stimulus by opening the mouth and making sucking movements (205).

It may be suggested that the spontaneous occurrence of genital tumescence tends to elicit manipulatory responses, that these in turn result in detumescence accompanied by relief of tension, and that the resultant stimulus-response association is strengthened by each repetition. In such a case regular habits of auto-genital stimulation could become firmly established in infants as soon as neuro-muscular development was sufficient to permit localization and repetitive manipulation of the genitalia.

HORMONAL FACTORS IN SEXUAL BEHAVIOR. Many observational and experimental findings combine to indicate that various hormones, particularly those of gonadal origin, may exert pronounced effects upon the sexual behavior of male and female mammals. Earlier reviews provide comprehensive summaries of the literature on this topic (49, 86, 91, 288), but the pertinent data will be surveyed in a somewhat different manner in the present article. In preceding sections an attempt has been made to define the neuro-physiological factors responsible for courtship and mating, and it has been stated in passing that the functional capacity of certain nervous mechanisms is influenced by endocrine products. It now becomes necessary to consider the evidence upon which such conclusions are based and to attempt to understand the ways in which glandular secretions may exert their specific behavioral effects.

A. *Relation of Gonadal Cycles to Mating Activity.* 1. *Normal cycles in lower mammals.* In males and females of seasonally breeding species and in females of polyestrous forms complete mating performance normally occurs when the secretory activity of the gonads is at or near the maximum (49). The heat responses of female rats (59) and guinea pigs (329) usually appear only when mature ovarian follicles are present, and a similar correlation exists in the case of other domesticated animals such as the cow (154) and horse (153). Males of these species are continuously active sexually and the secretory activity of the testes appears to be more or less constant; but in seasonally breeding forms like the marten (204) and deer (319) the male's rutting behavior coincides with the recrudescence of the testes.

Although a close positive relationship between high gonadal activity and overt

sexual behavior is a general rule in nearly all lower mammalian forms, some individual exceptions exist in most if not all species. Some female mink whose ovaries contain many large follicles refuse to receive the male (109);[18] and a few rats (59), guinea pigs (61) and cows (155) show normal ovarian cycles but never exhibit heat behavior. All strains of laboratory rats apparently contain an occasional male that never displays copulatory activity despite the possession of histologically normal testes and well developed accessories (40).

In the majority of sub-primate species the pregnant female is not sexually receptive, but exceptions to this rule are evidenced by reports of frequent copulation shown by gravid golden hamsters (62) and rabbits (158). In the latter species, as a matter of fact, willingness to receive the male bears no observable relation to fertility, for it has been found that in the wild rabbit, *Oryctolagus cuniculus*, males copulate twice as often with pregnant or diestrous females as with those which are capable of insemination (63a).

2. *Induced cycles in lower mammals.* By the administration of gonadotrophic substances it is often possible to induce unseasonal development of the gonads, and the consequent increase in gonadal hormones results in the appearance of mating responses in female ferrets (130), sheep (85), swine (332), horses (90a, 93a, 157), cattle (154), cats (126, 219), dogs (189a) and rodents (112, 320). It should be added, however, that although follicle growth and ovulation occur in a high percentage of females subjected to gonadotrophic stimulation, the induction of estrous behavior is achieved in a smaller proportion of cases (235a).

Gonadotrophic stimulation of the immature testis or ovary may evoke the secretion of endogenous gonadal hormones which in turn cause precocious sexual activity. For example, female mice injected with fresh pituitary substance will mate at fifteen days of age, and rats subjected to the same treatment show all of the behavioral signs of estrus at twenty-two days although at this age they are so small that adult males cannot effect copulation (272). Female rats injected with chorionic gonadotrophin on the twenty-second day after birth mate and conceive three days after treatment (83), and administration of anterior pituitary extracts to immature male rats is reported to result in "premature psychic maturation" (283).

Findings of this nature indicate that the neuro-muscular factors involved in adult sexual behavior are functionally organized long before the advent of reproductive maturity, and that the activation of these mechanisms merely necessitates the presence of adult hormone levels. As a matter of fact there is one bit of evidence to show that in some species adult mating responses are possible immediately after birth. For the first few post-natal hours female and male guinea pigs respond to tactile stimulation of the rump with the execution of lordosis and opisthotonus in a manner typical of the sexually-receptive adult female (60). Presumably these reactions occur under the influence of temporarily surviving maternal hormones; in any event they disappear within the first day after birth.

[18] In this species there appears to be little direct correlation between waves of developing follicles and willingness to copulate (109).

3. *Normal cycles in primates.* The interrelationship between ovarian cycles and sexual behavior is less clear-cut in the intermediate and higher primates than in lower mammals. In more primitive primates such as the lemuroids the female's receptivity apparently is still heavily dependent upon gonadal hormones, for the female galago, *G. senegalensis mohli* will mate only during physiological estrus (193a). Among the monkeys, however, the situation is altered slightly, for although the female rhesus is fully receptive only at the time of ovulation (20) she may permit copulation during other stages of the cycle (75), and her readiness to accept the male is affected by social and behavioral factors as well as by her own physiological status (76). Even greater independence from ovarian conditions is to be seen in the sexual activities of female apes. The chimpanzee may display sex presentation and receive the male at any point in the menstrual cycle (309, 324, 326), and although marked individual differences undoubtedly exist, it appears that this primate stands midway betwen the monkey and human as regards the degree to which ovarian condition affects social behavior (330).

It has proven extremely difficult to identify possible effects of ovarian cycles upon sexual responsiveness in the human female, but it seems fairly certain that hormonal influences are much less important in our own species than in any lower form. Various investigators have reported that most women experience maximal sexual excitability just before and just after the period of menstrual flow (93, 96, 299), but non-hormonal factors undoubtedly contribute materially to any such variation in desire for intercourse.

Incomplete as they undoubtedly are, the available data strongly suggest the existence of an inverse relationship between advancing phyletic status and the degree to which the female's sexual behavior is controlled by ovarian hormones. The full significance of this observation becomes apparent when it is considered in conjunction with previous statements concerning the evolutionary increase in the importance of cerebral functions to the sexual activities of mammals.

B. *Effects of Gonadectomy.* Direct evidence for the function of testicular and ovarian hormones in sexual behavior is provided by descriptions of behavioral changes which follow removal of the reproductive glands.

1. *Removal of the ovaries.* The effects of ovariectomy upon mating behavior vary according to the phylogenetic status of the species, and in higher mammals individual differences are apparent. In female rodents (165, 296, 315), ungulates (7, 211), and carnivores (22, 181, 189, 197) the operation occasions prompt and complete elimination of copulatory reactions.

In the female rhesus monkey sexual responsiveness ordinarily is lost rapidly after ovariectomy (13), but under special conditions, such as those consequent to specific types of brain injury, copulation may occur frequently despite gonadectomy (177). Female chimpanzees tend to show sexual presentation and permit copulation many months after loss of the gonads, although the residual behavior is less frequent and prolonged than that occurring during the ovulatory period in intact animals (80).

The sequelae to human ovariectomy are in dispute. According to different authors this operation may increase (203), decrease (81, 124, 162, 202), or have no effect upon sexual desire in women (115, 312). The lack of agreement between

authorities strongly suggests that individual differences are marked and that hormonal effects are much less powerful and less direct in the sex life of the human female than in that of lower forms.

2. *Removal of the testes.* The effects of castration upon sexual behavior in male mammals differ with the species, with the individual, and with the age of the animal at the time of operation.

a. *Pre-puberal castration.* It is sometimes stated that male animals gonadectomized before puberty exhibit no mating behavior (86), but the limited applicability of this generalization is indicated by reports of frequent if incomplete copulatory reactions in pre-puberally castrated male rats (38) and guinea pigs (218, 265, 275). The responses observed in such animals usually consist of mounting the receptive female and exhibiting pelvic thrusts. Erection does not seem to occur very often, intromission is infrequent, and ejaculation is lacking (50). Pre-puberally castrated male chimpanzees show much more sexual activity than do similarly operated rodents, and at least some adult apes deprived of testes in infancy are capable of frequent copulation with erection and intromission (79).

b. *Castration in adulthood.* Male mammals from which the testes are removed in adult life may continue to display coital reactions for many months after operation. Casual observation has shown that copulatory behavior survives castration in male horses (277), cattle (307), and monkeys (308), although no data have been reported which would indicate the completeness or intensity of the residual sexual activity. Quantitative studies of pre- and post-castrational mating performance in male rats (46, 268, 277, 291, 296) and rabbits (293) reveal that ejaculation is the first element of the pattern to disappear following gonadectomy, that complete copulation with intromission undergoes a progressive decline in frequency, and that in some males of both species incomplete copulatory attempts persist for several months.

The changes which follow castration in adulthood appear to include a reduction in the drive to seek out the sexually-receptive female, for gonadectomized male rats are less willing than intact animals to cross an electrified grid interposed between them and the estrous female (226); and castrated male guinea pigs display a weakening of the tendency to cross a mechanical hurdle with a female in heat on the other side (265).

The plethoric and contradictory literature dealing with sexual ability in castrated men permits only two generalizations. The range of individual variability is definitely wider in humans than in any other mammalian species (182), and the importance of testicular hormone for susceptibility to arousal and capacity for complete response is less marked in man than in lower forms (216). Some authorities adhere to the extreme view that testis secretions are entirely dispensable, and that "pre-pituitary" and "psychic centers" control libido and potency in the human male (113). The majority of writers, however, concur in the belief that, although their effects may be less important in human sex life than in that of lower animals, gonadal secretions do play a major rôle in the normal sex behavior of man (240, 285, 302).

References in the medical literature report complete survival of sexual powers

in various individual cases studied nine, twenty (257), and thirty (113) years after loss of the testes. In other instances gradual loss of desire and capacity for intercourse is said to have become evident at different intervals from two months to seven years after operation (87, 210, 213). Some castrates report that although the ability to achieve orgasm is reduced or eliminated, sexual desire and the capacity for erection are not affected; and it will be recalled that in the case of male rats and rabbits the ejaculatory response was found to be the most sensitive indicator of post-operative hormonal deficiency (50, 293, 296).

Partial or complete retention of sexual powers after castration might be interpreted as a result of androgenic stimulation provided by hormones of the adrenal cortex; but it is doubtful that any such explanation is universally applicable, for male castrates with very low titers of urinary androgen may perform coitus several times weekly as long as thirteen years after loss of the testes (152).

A major obstacle to estimation of the effects of castration upon sexual activity in men arises from the widely recognized influence of non-hormonal factors which may affect susceptibility to arousal and capacity for intercourse. Repeated references to the power of "suggestion" and "psychological factors" reflect a general acceptance of the fact that in the human as in no other animal the cortical component is of primary importance in the control of sexual phenomena.

C. *Effects of Administering Gonadal Hormones.* Observed correlations between cycles of secretory activity within the gonads and periodic appearance of sexual behavior, and the recognized effects of castration upon mating tendencies lend considerable support to the belief that ovarian and testicular hormones are in some fashion responsible for courtship and mating in many species. Even more direct evidence for such a conclusion is to be seen in the behavioral changes which follow the administration of gonadal hormones to male and female mammals.

1. *Ovarian hormones in the female.* Many reports describe the appearance of sexual receptivity in spayed or anestrous female mammals consequent to the administration of ovarian hormones. Injections of estrogen evoke mating responses in the anestrous cow (157, 321) and ewe (84, 155, 156), and in the spayed bitch (181, 189), cat (22, 197), ferret (206), ewe (21), cow (1a), and rhesus monkey (13). Administration of estrogen to spayed chimpanzees causes swelling of the sex skin and intensifies the tendency to court and cohabit with the male (80). It may be of considerable significance that the intensity and completeness of the sexual pattern induced by exogenous estrogen is related to the amount of hormone administered. For example, spayed heifers receiving estrogen exhibit parts of the pattern after one or two treatments, but continued dosage is essential if all of the normal pattern is to be evoked (1a).

Ovariectomized females of some species, including the guinea pig (58, 61, 165), golden hamster (123), mouse (252), and rat (39), show sluggish heat reactions when treated with estrogen, and normal estrous behavior appears only if estrogen administration is followed after a suitable interval by the injection of progesterone. In other species progesterone appears to act as a sex depressant. Thus, female rabbits in estrus may refuse to mate following progesterone admin-

istration (200), and the estrogen-induced heat of the spayed rhesus female is reduced by injection of progesterone (19).

Individual differences in the behavioral response to hormone treatment have been noted in several species. For example, spayed ferrets vary with respect to the amount of estrogen which must be injected to obtain full behavioral estrus (206), and the same is true in the case of cattle. In general it appears that individuals which exhibit the most intense and complete sexual activity prior to ovariectomy respond post-operatively to lower concentrations of exogenous hormone than do other females whose pre-operative mating reactions were less easily elicited. In one experiment the mating performance of a group of heifers was observed before castration, and when estrogen was given post-operatively it was found that, "in general . . . the easier it had been to detect heat [pre-operatively] the lower was the level of hormone necessary to induce heat after the operation" (7).

It has been noted above that there are in various species a few individual females which show normal ovarian cycles but never come into behavioral estrus. When female guinea pigs of this type are ovariectomized and injected with ovarian hormones sexual behavior may be elicited if very large doses are employed (61), and some heifers that have never shown heat behavior will do so following the administration of very large amounts of estrogen (157). Findings of this nature make it possible to assume that the original failure of normal sexual receptivity was due, not to a sub-normal supply of gonadal hormone, nor to incompletely organized nervous mechanisms, but to the fact that the neural circuits lacked normal sensitivity to the facilitating effects of physiological concentrations of the essential endocrine secretions.

There are certain observations which indicate that comparable individual differences are to be found among female chimpanzees. In one study (80) four ovariectomized apes were treated with estrogen and three animals became very active sexually, showing mating behavior identical to that of intact females at the height of genital swelling. The fourth female exhibited the expected swelling of the sexual skin but would not receive the male; and consultation of breeding records revealed that prior to ovariectomy this particular individual had never permitted males to copulate.

The fact that in the human female sexual responsiveness is correlated loosely if at all with cycles of estrogen production, and the prevalence of contradictory reports concerning the sequelae to ovariectomy in women would not lead us to expect any general agreement as to the effects of hormone treatment in ovariectomized women. However, it is reported that following this operation some women continue to display satisfactory marital adjustments only if estrogen is administered (135). In one study seven oophorectomized women received estrogen. Five patients experienced a restitution of libido which had been lost post-operatively, one case in which pre-operative responsiveness had been low described a marked gain under treatment, and the seventh patient reported post-operative loss with no improvement under hormone (161). Attempts to increase post-menopausal responsiveness by hormone therapy have not been

successful to any degree, and in general clinical results suggest that any concept of human sex drive as solely dependent upon ovarian secretions is "an oversimplification of an extremely complicated and subtle reaction" (267). The major importance of psychological factors is strongly indicated by reports of sexual rehabilitation resulting from psychiatric treatment (91).

In connection with the depressing effects of progesterone upon estrous behavior in some lower mammalian species it is of interest to note that this hormone is said to decrease the desire for intercourse in women (146).

2. *Testicular hormone in the male.* Androgen administration results in the restoration of normal copulatory behavior in pre- or post-puberally castrated male rabbits (125), guinea pigs (219, 265, 275), and rats (219, 266). The progressive change in sexual behavior which accompanies daily treatment of castrated male rats is precisely the reverse of the modifications that follow removal of the testes. Initial injections evoke an increase in the frequency of incomplete matings. Continuation of hormone treatment calls forth complete copulation with intromission, and lastly the ejaculatory response is restored (46, 50, 296). Data of this sort illustrate the important point that the intensity and completeness of sexual behavior depend in part upon the level of gonadal hormones, a conclusion corroborated by reports of several investigators (71). For example, although in the absence of hormone treatment the pre-puberally castrated male chimpanzee may display frequent copulation with intromission, the administration of androgen is necessary to the occurrence of ejaculation (79).

It is abundantly clear that the concentration of testis hormone just adequate to elicit a given mating response in castrated males varies from one animal to another, and individual differences of this sort are definitely related to sexual responsiveness prior to operation (50, 296). In tests conducted before hormone treatment pre-puberally castrated male rats exhibit wide differences in responsiveness to the receptive female; and when testosterone propionate is administered individuals that were highly reactive prior to treatment tend to copulate at lower dose levels than do those which showed little or no sexual activity in the absence of androgen (46). This observation suggests that males which respond to comparatively small amounts of hormone are individuals in whom the nervous mechanisms for sexual arousal are relatively excitable even when hormonal facilitation is lacking.

Among males as among females there are some individuals who fail to show sexual behavior although the histological condition of the accessory organs indicates that gonadal hormones are secreted in normal amounts. Male rats of this type sometimes copulate when the concentration of endogenous hormone is augmented by administration of androgen (31, 294), and this suggests that the original failure to mate may have been due to relative insensitivity to normal hormone level on the part of the neural mechanisms involved in arousal and manifestation of sexual excitement.

It has been recorded that some human males suffer noticeable reduction in sexual capacity and desire following loss of the testes; and in many such cases the administration of androgenic hormone results in increased frequency of erection,

intensification of sexual drive, heightened capacity for intercourse, and the appearance of erotic dreams (73, 141, 303). It is worthy of note that in men as in the males of other mammalian species the degree to which normal sexual function is restored varies with the dose level of the hormone (150, 241).

3. *Response of immature animals to gonadal hormones.* At an earlier point it was noted that pre-pubescent males and females may display adult copulatory responses when the immature gonads are stimulated to precocious secretory activity by the administration of gonadotrophins; and here it can be added that similar behavioral changes are evoked by direct application of gonadal steroids. Sexual mounting appears in male rats as early as sixteen days after birth when androgen is administered on the fourteenth day; and females injected with estrogen show lordosis at twenty-one days, although in the normal course of development this response does not appear until a month or so later (43).

In like fashion the administration of estrogen to the immature bitch is followed by the appearance of all signs of estrus including willingness to accept the male (189). Copulatory behavior has not been observed, but there is proof that the sexually-stimulating qualities of the very young female chimpanzee are markedly increased by estrogen treatment. Although adult males show little sexual interest in normal infantile females, proximity to an estrogen-injected female less than two years old is reported to have elicited intense excitement in an adult male as evidenced by the prompt occurrence of erection followed by masturbatory responses with ejaculation (104).

The facility with which testicular and ovarian hormones stimulate adult copulatory performance in immature rodents points again to the conclusion that the neuro-muscular organization for such reactions is completed long before mating behavior normally appears, and that the absence of any feminine responses in pre-adolescent females and the incomplete nature of the pre-pubescent male's sexual activity are due primarily to lack of appropriate hormonal facilitation.

Although the mechanisms for mating appear to be completely organized relatively early in life, and although they frequently can be rendered functional under the influence of exogenous hormones, their sensitivity to hormonal effects is not fully developed during the period of infancy. On the contrary, behavioral responsiveness to endocrine secretions appears to be low in the very young infant and to increase post-natally in much the same fashion as does the sensitivity of such other elements in the reproductive complex as the uterus, vagina, prostate and seminal vesicles (243).

New-born guinea pigs respond to tactile stimulation of the rump with the exhibition of lordosis and opisthotonus in a manner typical of the adult estrous female (60), and this indicates that the essential neuro-muscular units are fully organized pre-partum. Presumably the post-partum heat responses, which persist for only a few hours, are due to the temporary effects of maternal hormones. In any event it has been shown that females seven days old fail to display heat responses when injected with ovarian hormones, even though the dosage be very high. Examinations repeated at regular intervals show a rapid increase in

sensitivity to the hormones with maximal responsiveness appearing at about thirty days after birth and continuing for two years (316). The progressive change in reactivity is not due to endogenous ovarian secretions, for it occurs in individuals spayed at birth. The female rat is similarly refractory to ovarian hormones during infancy, and in this species maximal sensitivity is also attained about the thirtieth day after birth (316).

I have suggested quite tentatively that the absence of mating behavior in pre-puberal females of lower mammalian species, and the relative infrequency and incompleteness of copulatory responses in males of the same species are due, not to nervous system deficiencies, but to lack of appropriate hormonal facilitation. Now if, for the purpose of exposition, this view is accepted, it provides supplementary evidence in connection with previously-mentioned differences in the extent of pre-puberal sexual behavior shown by primates and non-primates. There is, so far as I am aware, no reason to believe that the testes and ovaries reach an adult level of secretory function at an earlier developmental stage in primates than in non-primates; and accordingly the more complete copulatory activity of immature male and female monkeys, apes and humans may be interpreted as a function of the relatively greater importance of cerebral factors in the sexual life of higher forms.

D. *Hormonal Factors in Bisexual Mating Behavior.* In a preceding section of this review it was pointed out that under certain conditions male and female mammals may display portions of the mating pattern of the opposite sex. Such behavior has commonly been "explained" as a product of heterologous gonadal hormones, and rarely has sufficient emphasis been placed upon other variables which are equally powerful in determining the type of sexual activity that will occur in a given situation. From what has been said previously it should be apparent that the appearance of a particular mating response is affected by the pattern of external stimulation and by the functional characteristics of the neuro-muscular constitution as well as by the chemical nature of the facilitating hormonal agents. Only when all of these factors are taken into account is it possible to formulate an adequate interpretation of the execution of masculine reactions by genetic females and feminine responses by males.

At this point it will be profitable to consider first the hormonal interpretations of bisexual behavior, and then to consider a more comprehensive analysis based upon less restricted views of the physiological basis for such phenomena.

1. *Concepts of specificity and antagonism in the behavioral effects of ovarian and testicular hormones.* Evidence derived from a variety of sources has led to the formulation of theories which hold that the effects of gonadal hormones are highly specific, that only ovarian hormones can stimulate female morphological and behavioral characters, while testicular secretions are solely responsible for masculine bodily structures and overt reactions (192, 217).

a. *Spontaneous or experimental gonad reversal.* Transformation of an ovary into a testis and the converse change are fairly common occurrences in members of some sub-mammalian classes (82, 89), and morphological alterations of this type are sometimes accompanied by corresponding reversal of the overt sexual behavior. Experiments with mammalian material suggest that surgical ex-

change of masculine and feminine gonads may induce like results. Ovariectomized does bearing implanted testes behave sexually like the mature buck (191), and castrated male rats (278, 279, 280) or guinea pigs (274, 282) into which ovaries have been grafted exhibit estrous responses typical of the females of their species. Spayed female guinea pigs containing active testicular grafts respond to normal estrous females by displaying many elements of the masculine mating pattern (215, 282).

b. *Administration of heterologous gonadal hormones.* Changes which are reported to occur in mating behavior following the administration of androgen to females and estrogen to males lend support to the belief that gonadal secretions exert highly specific influences upon sexual activities.

The administration of androgenic preparations occasions the appearance of certain masculine copulatory responses in female rats (15, 180, 295), rabbits (170), dogs (54), and sheep (84); and castrated male rats treated with estrogen show various elements of the female mating pattern (14).

This sort of evidence indicating a high degree of specificity in the behavioral effects of ovarian and testicular hormones is buttressed by additional data which suggest that the execution of masculine sexual reactions is inhibited by estrogen, while androgen tends to depress feminine mating responses (282). It is stated, for example, that the responsiveness of male dogs to the bitch in heat is lowered by estrogen treatment (222); and men given estrogenic substances are said to experience a decrease in sexual desire (100, 121, 220).

2. *Evidence against concepts of antagonism or complete specificity.* Although there is no doubt that the behavioral effects of androgen and of estrogen are quite distinguishable and relatively specific there are definite limits to such specificity; and theories of antagonistic action are definitely questionable.

a. *Mating behavior of intersex individuals.* Intersex pigs with feminine external genitalia and lateral hermaphroditismus always attempt to copulate in masculine fashion although they may display some of the signs of estrus (26); and hemi-castrated male guinea pigs with one testis and one implanted ovary mate in masculine or feminine fashion, "according to the animals with whom they are brought into contact" (259, 281). I have recently discovered in my animal colony several Norway rats in which the external genitalia consist of a greatly hypertrophied clitoris and a penetrable vaginal opening. The internal reproductive organs of some of these individuals include one ovary and an ovitestis. Mating responses are bisexual, and either male or female copulatory patterns may appear under appropriate external stimulation.

The sexual behavior of intergrade pigs and of naturally-occurring or experimentally-produced hermaphroditic rodents shows that individuals bearing testicular and ovarian tissue may display overt mating reactions of both sexes, and such observations are difficult to reconcile with any concept of antagonism between the behavioral effects of ovarian and testicular hormones. How then are we to interpret the reported inhibition of masculine sexual behavior by estrogen administration, and the diminution of feminine mating reactions by androgen?

In the first place, none of the experimental reports describing results of this

nature include satisfactorily objective or quantitative behavioral records to support the conclusions advanced; but even if such data were available, the claim for an antagonistic effect of heterologous hormones would not be justified. A more reasonable interpretation rests upon the established fact that administration of exogenous gonadal steroids tends to depress the gonotrophic functions of the anterior pituitary and thus to interfere with the production of endogenous testicular or ovarian secretions (217).

The explanation proposed here would account for an observed decrease in sexual behavior following treatment with heterologous hormone as a result of lowered concentrations of endogenous gonadal agents. Support for this interpretation is found in reports that the implantation of ovarian tissue in the intact male guinea pig is followed by a decrease in the secretion of testicular androgen (270). Furthermore, men in whom sex drive has been lowered by estrogen treatment may experience a revival of libido when gonadotrophic substances are administered (142),—a result strongly suggestive of initial interference with hypophyseal stimulation of the testes.

b. *Bisexual reactions in morphologically normal animals.* Even more convincing evidence against theories of extreme specificity or antagonism in the behavioral effects of gonadal secretions is to be found in descriptions of masculine mating responses shown by morphologically normal female mammals and, less frequently, the display of feminine sexual reactions by untreated males.

At an earlier point in this review I have referred to the male-like mounting and execution of pelvic thrusts shown by female rats (18, 29, 36, 51, 163, 180), hamsters (reviewer's observations), guinea pigs (329, 331), rabbits (158), porcupines (265a), short-tailed shrews (232), marten (204), dogs and cats (reviewer's observations), African lions (88), swine (3), cattle (327), rhesus monkeys (76, 149) and chimpanzees (55, 325). Some writers have suggested that this type of behavior in females is caused by androgen (163), possibly of ovarian origin (284). However such suggestions seem to be based upon no more than an *a priori* assumption that the appearance of masculine sexual responses demands the presence of androgen.

There are several lines of evidence which seem to argue against the theory that masculine coital responses in the female are a product of ovarian androgen. For example, spayed heifers display mounting behavior (which is a common element in the normal estrous pattern of this species) when they are injected with estrogen (1a). The male-like mounting responses of the female guinea pig are dependent at least in part upon ovarian secretions, for the frequency of such reactions is correlated with the number of maturing follicles (329). In addition, this behavior is induced in the spayed female by the administration of estrogen and progesterone; the same hormones which elicit sexually-receptive reactions (331). However, although the female's masculine sexual activity and feminine receptivity seem to be controlled by the same endocrine substances, it is important to note that in some individuals the male behavior appears in the absence of heat (328); a finding which has been taken to indicate that different nervous mechanisms are involved (327). Ovarian secretions are not essential to mas-

culine copulatory responses in the female rat. There is no relationship between such behavior and willingness to receive the male, and the frequency of male reactions is not affected by pre- or post-puberal ovariectomy (51).

Feminine mating reactions are sometimes shown by male rats (29, 289), hamsters (reviewer's observations), rhesus monkeys (149) and chimpanzees (55). Only in the rat has the hormonal basis for such behavior been studied (47). The single animal described responded to receptive females with prompt and vigorous copulation, and reached the point of ejaculation much more quickly than the majority of males of the same strain. When mounted and palpated by other males the experimental animal shifted immediately to the feminine coital pattern. The feminine reactions were intense and complete and included hopping, ear-vibration and deep lordosis.

When the male was castrated the feminine mating reactions disappeared in less than a week, while masculine sexual reactions underwent the gradual decline which is characteristic in the adult castrate. Subsequent administration of androgen revived masculine copulation and ejaculation, and restored most of the feminine reactions although the latter were sluggishly executed. Injections of estrogen and progesterone evoked the complete feminine pattern as well as most of the masculine responses, but the ejaculatory reflex was lacking.

It appears that prior to operation both feminine and masculine sexual patterns were supported by testicular secretions; and the results of post-operative hormone treatment further indicate that androgen was capable of stimulating both types of behavior. The capacity of ovarian hormone to facilitate female behavior is in accord with evidence presented earlier; and the partial revival of masculine reactions under the influence of these substances receives more detailed consideration in the following paragraphs.

c. *Paradoxical effects of gonadal hormones.* Simplified theories proposing complete behavioral specificity of estrogens and androgens are further thrown into question by experimental data which demonstrate that feminine sexual behavior may be increased by administration of androgen and that masculine reactions are sometimes intensified under the influence of estrogenic treatment.

Pre- or post-puberally castrated male rats characteristically show incomplete mating responses, and complete copulations occasionally occur. If estrogen is injected the frequency of both incomplete and complete contacts rises noticeably, although the ejaculatory reaction is not revived (14, 37, 38). Estrogen has been observed to evoke male behavior in females as well as males. Anestrous ewes treated with estrogenic hormone tease and ride other females in masculine fashion (156, 157, 211), and the implantation of estrogen pellets in heifers is sometimes accompanied by such bull-like behavior as roaring, pawing the ground with the fore-hoofs, and pursuing and mounting estrous females (157). The masculine copulatory reactions of these estrogen-treated females include pelvic movements so vigorous that they culminate in a high proportion of pelvic fractures (119, 120). Removal of the hormone pellets is followed within three or four days by disappearance of the masculine sexual responses.

Complementary data are found in reports of the stimulation of feminine

copulatory performance by androgen. Untreated, spayed female rats show no estrous reactions. If androgen is injected into such animals they exhibit strong tendencies toward the masculine sexual pattern in response to receptive females, and, in addition, they display lordosis when mounted by other rats (18, 37, 163). Some clinicians report that lack of sexual desire and low responsiveness in intercourse may be treated more effectively in the human female by androgen than by estrogen (145, 147, 258). Androgen may also facilitate feminine sexual performance in the genetic male, for normal male rats injected with massive doses of testosterone propionate continue to execute masculine coital responses to the estrous female and begin to display feminine reactions when mounted by other males (33).

3. *Hormones and human "homosexuality".* The term "homosexual" has been employed in so many different frames of reference and with so many different connotations that its scientific validity is questionable, and its use is apt to detract seriously from a clear understanding of human sexual behavior. It would be fruitless in this discussion to attempt any original definition, or to describe the variety of contradictory definitions which have been sponsored by earlier writers. For present purposes it is sufficient to observe that there are human adults who appear to be capable of sexual arousal and genital activity only when stimulated by members of their own sex, and who feel either indifference to or active revulsion for heterosexual contacts. On strictly hypothetical grounds some writers have attempted to account for such behavior in terms of an insufficiency of homologous gonadal hormone and/or a hyper-normal concentration of heterologous secretions (133, 134, 140, 167, 194, 238). This theoretical point of view is difficult to reconcile with the consistent failure of attempts to "cure" the condition by hormone treatment (297), and with the additional fact that administration of androgen to male homosexuals tends to increase the frequency of their sexual activity with other men (134).

Recognition of the obvious contribution of experiential factors to the structuring of human sexual activity raises serious doubts as to the directive influence of gonadal hormones in homosexuality (110, 130). The guiding effects of training and experience are reflected in the fact that the preferred sex rôle and the direction of sexual desire in human hermaphrodites tend to be in accordance with the up-bringing of the individual (as a "boy" or "girl"), and are relatively independent of internal or external reproductive morphology (116). One study of 84 "pseudo" and "true" hermaphrodites revealed a high correlation between the form of overt sexual expression and the manner in which the person had been raised; whereas there was a much less marked relationship between sexual behavior and the character of the gonads. The author interpreted his findings to mean that, "while the *power* of the human sex drive may possibly be largely dependent upon physiological factors, such as the quantity and/or quality of sex hormone secretion, the direction of this drive does not seem to be directly dependent upon constitutional elements" (106).

The potent influence of individual experience is not restricted to overt sexual behavior, but affects equally the more generalized expressions of sex such as those measured in psychological tests of "masculinity" and "femininity."

Application of the Terman-Miles "M-F" test to human sex intergrades revealed that in many cases the final score inclined heavily on the side contrary to biological sex (305).

E. *Rôle of Non-Gonadal Hormones in Sexual Behavior.* The conclusion is inescapable that the secretory products of several endocrine glands must exert indirect influences upon the sexual behavior of male and female mammals, but supporting evidence as yet is scanty.

1. *Anterior pituitary.* Pituitary control of sexual activity appears entirely indirect, being limited to the stimulation of secretory activity within the gonads. This influence, however, is of primary importance; and hypophysectomy eliminates mating in the male rat (250, 274) unless the testes are maintained by administration of gonadotrophic substances (273). The possibility that the gonadotrophins might be directly essential to sexual behavior is contra-indicated by the survival of normal mating reactions in hypophysectomized male rats (150, 225) and female cats (198) treated with testicular and ovarian hormones respectively.

2. *Adrenal cortex.* Steroid hormones secreted by the adrenal cortex are known to possess certain androgenic properties (68), and it has been suggested that some cases of survival of sexual behavior in castrated men may be due to cortical androgens (151). Although it is purely speculative a comparable explanation might account for the masculine copulatory behavior shown by ovariectomized female rats (51). The latter point is one which could and should be attacked experimentally. It will be recalled that progesterone is reported to depress sexual desire in women, and at this point it may be added that desoxycorticosterone acetate is said to exert similar effects (146).

3. *Thyroid.* Thyroid secretions appear to affect sexual activity primarily if not exclusively by way of systemic changes in metabolic function. Male rats display no mating behavior after removal of the thyroid, but thyroidectomized females of this species are capable of fertile breeding (118, 251). This may be compared to similar inter-sexual differences in the importance of the cerebral cortex to the copulatory activity of male and female rats. It appears probable that thyroidectomy is followed by reduction of general activity and lowered responsiveness to external stimulation in male and female alike; but because hers is the more passive mating rôle the female's sex reactions may be adequate for reproduction despite such loss; whereas in the male the depressing effects of the hormonal deficiency obviate the occurrence of sexual arousal which is essential to his copulatory performance.

A pre-puberally thyroidectomized bull is reported to have shown complete lack of mating behavior in adulthood (233). Ejaculates obtained from this animal were used successfully in artificially inseminating estrous cows, and this indicates that the spermatogenic functions of the testes were normal. Sexual arousal and copulatory behavior followed the administration of desiccated thyroid, dinitrophenol or testosterone propionate and the variety of the effective substances suggests that initial lack of sexual excitability was merely one reflection of a generalized metabolic disturbance.

4. *Thymus.* Presently available evidence give us little reason to believe that

the thymus has anything to do with sexual behavior. Removal of this body during infancy has no effect upon the breeding behavior of male or female rats during adult life (237). Although one experimenter has concluded that administration of thymocrecin reduces sexual responsiveness in the estrous female rat, the published report includes no quantitative measures of sexual receptivity, and both experimental and control groups were very small (70).

F. *Locus and Nature of Hormonal Action.* Evidence concerning the ways in which glandular secretions bring about changes in behavior is fragmentary and in most cases inferential, but a brief exposition of the principal recognized and suspected types of hormonal influence will serve to illustrate the problems involved and may suggest potentially fruitful areas for future investigation.

By virtue of their systemic effects products of several endocrine glands exert indirect control over the behavior of organisms. For example, because of their profound influence upon metabolic processes, secretions of the thyroid are essential to any and all behavioral responses which depend upon normal metabolic function. In the present discussion, however, such generalized glandular effects will be taken for granted, and attention will be confined to the more specific influences exerted by testicular and ovarian hormones upon courtship and mating.

1. *Loci of action.* a. *Extra-neural effects.* Gonadal hormones stimulate growth and development in various secondary sex structures which subsequently are employed in the execution of behavioral responses. Such effects are particularly evident in sub-mammalian forms. The advent of breeding coloration and gonopod development in certain fishes, hypertrophy of nuptial pads and vocal apparatus in male salentia, extrusion of "courtship teeth" in salamandria, and development of the copulatory organ in male birds of the order *Ansiformes* depend upon secretions from the sex glands (49).

Though usually less prominent, the secondary sex characters of mammals are in many cases under the influence of testicular or ovarian hormones. The final stages of antler growth in the male Virginia deer depend upon testicular androgen (319), and during the rutting season the buck employs these hormonally-stimulated structures in his battles with other adult males. The outstanding example of specific growth effects produced in mammals by testicular and ovarian hormones is seen in the stimulation exerted by these glandular products upon the accessory reproductive structures; and some authors seem inclined to believe that it is by this means exclusively that gonadal secretions affect behavior. Thus, one writer suggests that the most probable rôle of the testis hormone in the sex behavior of the rat is that of "fostering normal growth and development of the reproductive organs and perhaps maintaining a general 'sex tonus' " (314).

Such an extreme view is negated by evidence presented above to prove that sexual reactions may occur in the absence of the accessory reproductive tract. However, it is true that in the intact animal sensations arising from genital stimulation play an important part in the generation of intense sexual excitement. Furthermore it is known that gonadal hormones are essential to normal growth

of the copulatory organ. In the male rat, for example, penis growth is markedly inhibited by castration at birth. Animals subjected to this operation respond to androgen treatment in adulthood with the execution of numerous incomplete copulations; but because of their infantile phallic organs such individuals rarely achieve intromission and cannot attain the peak of arousal essential to ejaculation (50). Here then is an illustration of the indirect manner in which hormones may affect behavior by controlling the development of an essential effector structure, and it seems highly probable that additional examples of this type of effect will be demonstrated by future experimentation.

b. *Effects within the nervous system.* Gonadal hormones appear to exert the major part of their behavioral effect by way of the nervous system, although presently-available evidence does not permit any definitive statement as to the exact locus of hormonal action. It is conceivable that the sex gland secretions might influence behavior by altering the functional capacity of sensory receptors, but data to support such an assumption are lacking,[19] and the most probable loci of hormonal effects appear to lie within the brain and spinal cord.

Some experimentalists have concluded that estrogen controls mating responses in the female cat by virtue of its effect upon short-arc reflexes in the spinal cord (197); whereas other authorities prefer to believe that the influence of the hormone is exerted principally upon the integrative mechanisms of the diencephalon (24). Until our understanding of the neural basis for sexual behavior is more nearly complete, and until there is convincing evidence to indicate the limits of hormonal action, it would appear safest to assume that gonadal hormones affect all of the nervous units involved in mating activity.[20]

It has been explained that erection of the penis is mediated by low spinal circuits (23, 24), and there is reason to believe that androgen directly affects these primary nervous mechanisms. For example, completely decorticate male rats injected with large amounts of testosterone propionate exhibit constant erection, although they give no indication of sexual excitability and are totally unresponsive to the female in heat (46). Similar hormone treatment of the human male may be followed by priapism even in cases in which there is no increase in sexual desire (91).

It is clear that reproductive secretions also affect supraspinal levels, for studies of estrogenic effects in decerebrate female mammals indicate that ovarian hormones alter the functional capacity of midbrain mechanisms involved in the integration of the separate motor responses of copulation (24, 94).

[19] It has been reported that a condition of olfactory hyper-acuity occurs in women twenty-four to forty-eight hours before the onset of menstruation and persists until several days after the cessation of flow (107). Whether or not this altered sensitivity has any hormonal basis it is impossible to decide, but the possibility is evident.

[20] It seems probable, however, that sensitivity to hormonal facilitation varies from one sexual mechanism to another. It is known that different morphological sex characters require different amounts of gonadal hormone for normal development (235), and it is quite likely that similar differences exist between various behavioral units, with the result that a concentration of hormone sufficient to support one element in the total mating pattern may be too low to affect certain other segments of the sexual response.

Finally, it is to be noted that gonadal hormones influence activity within still other neural structures which contribute to sexual function without mediating any of the overt reactions comprising courtship or coition. When intact male rats are injected with androgen their responses to the estrous female are not materially altered. The promptness with which mating is initiated, the frequency of copulation, and the rapidity with which ejaculation occurs remain essentially unchanged. However, the hormone does exert a profound effect upon susceptibility to sexual arousal which is reflected in the increased variety of stimulus animals capable of evoking mating attempts on the part of hormonally-altered individuals. Thus, although untreated males are likely to mate only with the receptive female, the administration of testosterone propionate is followed by repeated and persistent attempts to copulate with diestrous female rats, anesthetized females, other males, and even with immature female guinea pigs (34). The tendency to become sexually aroused is markedly increased by androgen although the nature of copulatory reactions is not changed.

It seems probable that in humans the action of gonadal hormones upon higher nervous mechanisms may be at least partially responsible for the marked increase in erotic dreams described by castrates during periods of androgen treatment (91),[21] and for the increased pleasure in kissing and embracing members of the opposite sex which is often experienced under therapy (212).

2. *Nature of effect.* a. *Alteration of thresholds.* At the present state of knowledge theories concerning the probable nature of hormonal effects upon nervous tissue are highly speculative, but the more widely accepted suggestions deserve at least some consideration. Proposals that gonadal hormones "eroticise" the nervous system (71, 282), or "activate" (17) or "energize" (54) nervous patterns are too vague for objective analysis; but it is possible to deal critically with more explicit suggestions such as those to the effect that endocrine secretions actively stimulate nervous discharge in various circuits or centers (90, 249), or inhibit neural activity within one region or another (111, 168).

In the main, theories of the latter type receive only limited support, and the majority of writers on this subject have suggested that hormones neither stimulate nor inhibit nervous processes, but instead act as "sensitizers," lowering the threshold of particular neural elements to afferent stimulation (23, 40, 187, 230, 253, 265, 331). Direct support for hypotheses of this nature is lacking although some suggestive data are available. It is known, for instance, that in cases of adrenal insufficiency the irritability of the sympathetic system is drastically reduced (159).

b. *Basis for selective action.* Even if it were possible to demonstrate conclusively that one hormone increases the stimulability of nervous tissue whereas another fails to do so, there would remain the necessity of explaining the relatively specific behavioral effects exerted by secretions from different glands. Any adequate theory would have to account for the fact that in either males or fe-

[21] Although part of this psychic change may be traceable to increased genital activity during sleep.

males androgen tends to enhance masculine sexual reactions, while estrogen affects primarily the feminine mating pattern.

In essence this means that a particular biochemical agent exerts a strong effect upon one nervous mechanism and has at most only a mild influence upon a second one; while a different chemical substance is without effect upon the first mechanism but plays intensely upon the other neural circuit. Neuro-chemical relationships of this general type are well known in physiology. Various analgesics such as cobra venom reduce the sensitivity of nerve endings for pain without affecting other types of cutaneous receptor organs (195). Presumably the differential response of various nervous elements to a given compound is due to biochemical differences within the nervous structures themselves, and if this is the case it provides an explanation for the relative specificity of hormonal effects upon behavior.

It is possible that the neural circuits and centers involved in the mediation of feminine copulatory responses differ not only structurally but also biochemically from those responsible for masculine sexual reactions. Furthermore, the mechanisms concerned with feminine coital performance may be, by reason of their characteristic biochemical properties, especially sensitive to estrogen; whereas the mechanisms for masculine responses, having a different biochemical constitution, may be assumed to possess an affinity for androgenic compounds.

When the castrated female is injected with estrogen the hormone reacts with the nervous elements contributing to feminine mating behavior in such a manner as to increase their sensitivity to afferent stimulation, and sexually receptive responses appear. In similar fashion androgen increases the sensitivity of the mechanisms for masculine behavior in the castrated male. At the same time both sexes possess central nervous arrangements capable of mediating mating responses typical of the opposite sex; and therefore when androgen is injected in the genetic female, or when estrogen is administered to the male, the particular nervous mechanism which is sensitive to that chemical substance reacts promptly and the corresponding sexual pattern appears under conditions of appropriate external stimulation.

SUMMARY

The evidence reviewed in foregoing pages serves first to emphasize the pressing need for more intensive investigation of the physiology and psychology of sexual behavior. Existing data are too fragmentary to support any final conclusions, but a recapitulation of the more important aspects of our subject can be formulated in general terms providing it is explicitly understood that all such generalizations are extremely tentative and may be subject to numerous exceptions. As a matter of fact, recognizing the many lacunae in present-day knowledge, and realizing the prevalence of contradictory findings, no author could hope that his interpretations would prove to be more than rough approximations of the truth.

A. *Neurological Evidence.* 1. Many of the discrete sensory-motor components of the complete copulatory pattern are mediated by nervous circuits lying within

the spinal cord. This holds true for males and females and for all mammalian species which have been studied. Various genital reflexes and certain gross postural adjustments characteristic of coital activity survive and can be experimentally elicited in chronic spinal preparations. In the normal animal these spinal mechanisms are of course subject to facilitative and inhibitive influences from higher nervous levels.

2. Integration of the separate response units into a biologically effective behavior pattern is achieved by supra-spinal nervous elements. In the case of female rodents, lagomorphs and carnivores this function is carried out by mechanisms lying above the cord and below the cerebrum. Certain relatively restricted hypothalamic regions appear to be intimately involved in this activity. In any event it is evident that decerebrate females of the above-mentioned orders are capable of fertile mating with normal males. This does not mean that the female's sexual behavior is unaffected by decerebration; nor does it indicate that the normal individual's coital performance is independent of cerebral influences. Evidence to the contrary is available.

3. Nothing is known concerning the identity of sub-cortical, supra-spinal mechanisms which may contribute to the integration of the male's sexual responses.

4. In male rodents the cerebral cortex appears to be indispensable to sexual arousal, although so far as is known this part of the brain makes no essential contribution to the organization of the motor acts of copulation.

5. Studies of male cats indicate that extensive neo-pallial injury interferes with various sensory-motor adjustments involved in coitus; and this undoubtedly is due to the fact that in carnivores the motor and sensory cortices have assumed a larger rôle in the control of all types of voluntary activity. The totally decorticate male cat shows no sexual behavior, and gives little or no evidence of excitement when placed with a receptive female. The absence of sexual response in the decorticate male cat stands in striking constrast to the survival of copulatory performance in the decerebrate female of this species.

6. The extensive dependence of finer sensory-motor co-ordinations upon cortical centers in the primates makes it appear probable that in the monkey, ape, or human large scale injury to the neo-pallium would render copulation exceedingly difficult if not impossible. However, experimental proof for this assumption is lacking.

7. It is known that stimulation of particular cutaneous receptors, located in the genitals and elsewhere, contributes in major fashion to the intensification of sexual excitement; but the stimuli involved in pre-contact arousal are less well understood.

8. There is little direct evidence to reveal the sensory basis for sexual arousal in female mammals. It is established that females of several sub-primate species are capable of fertile copulation after combined removal of the end-organs for vision, olfaction and audition; but it seems quite probable that a broader approach to the problem would reveal deficits in the total mating pattern of such drastically desensitized individuals. All that has been demonstrated is that

they respond appropriately to the stimulation provided by direct bodily contact with a sexually active male.

9. Sexual arousal in males of lower mammalian species appears to depend, not upon a single, critical type of sensory cue (such as odor of the female in heat), but upon a pattern of stimulation involving simultaneous and repetitive activation of several receptor systems. No single type of end-organ is essential providing others remain.

10. Incidental observations suggest that in male and female primates the arousal of complete sexual excitement ordinarily rests upon stimulation of most of the major receptor structures.

B. *Behavioral Evidence.* Laboratory experiments dealing exclusively with behavior, and non-experimental observations reported by clinicians, commercial animal breeders and others provide a heterogeneous body of data much of which supplements the neurological findings summarized above.

1. In many animal species there is a close behavioral relationship between sexual arousal and various other emotions. Sexual responses tend to appear in emotionally-charged but non-sexual situations, and a variety of types of excitement may lead to active sexual behavior. Conversely, susceptibility to normal sexual arousal is subject to inhibition by fear, anxiety, etc. Findings of this nature indicate a functional relationship between the central nervous mechanisms for sexual activity and other neural units involved in non-sexual emotions.

2. A series of inter-sexual differences between male and female mammals of several sub-primate species provides evidence which supports certain conclusions drawn from neurological investigations.

(a) The sexual arousal of the male tends to be inhibited in a strange environment, or in a familiar environment which has previously been associated with painful stimulation; but comparable inhibition occurs much less frequently in the female. An environmental context in which heterosexual copulation has been experienced exerts a facilitative effect upon sexual responsiveness in the male, but does not do so in the female. Once arousal has occurred the male becomes relatively unresponsive to extraneous, non-sexual environmental stimuli; whereas the female is capable of carrying out her sexual rôle and simultaneously attending to other aspects of the total situation.

(b) Among rodents, carnivores and ungulates the male begins to show incomplete copulatory responses long before puberty; while the female displays none of the adult feminine sexual pattern until the first estrus.

These and other differences between sub-primate males and females are thought to be due in large measure to the fact that the male's sexual behavior is intimately influenced by the cerebral cortex, while the mating performance of the female is less directly dependent upon the neo-pallium.

3. Certain inter-sexual differences and similarities in the mating behavior of male and female primates throw some light upon the nervous basis for reproductive life at higher levels of the mammalian scale.

(a) Male and female monkeys, apes, and humans indulge in extensive and

frequent pre-puberal sex play; and in young chimpanzees and children such behavior may proceed as far as heterosexual copulation with intromission and pelvic thrusts. This phyletic increase in precocious sexual manifestations is regarded as a product of the higher development of the cerebral cortex and the increasing importance of this brain region to the mating activity of both sexes.

(b) Reproductively mature but sexually inexperienced female chimpanzees which are placed with a breeding male during the period of fertility react to the consort's copulatory advances in biologically effective fashion, and coition usually is carried out without difficulty or delay. In contrast, sexually inexperienced adult males of this species seem unable to effect union with the receptive female at the first opportunity, and a long period of practice and learning is necessary before the male is capable of normal copulatory adjustments. This inter-sexual difference is taken to be a reflection of differential importance of higher nervous mechanisms in the coital activities of the two sexes.

4. Females of many primate and sub-primate species often mount other females that are in heat, executing pelvic thrusts and otherwise behaving in masculine fashion. Such females display no morphological abnormalities of the reproductive system, and the capacity for masculine copulatory performance is regarded as an integral element in the feminine behavioral repertoire. Males of several species respond to the sexual advances of other males with the display of feminine copulatory reactions. Individuals which exhibit temporary inversion of the mating rôle revert promptly to the coital pattern of their own sex when opportunity is offered. The evidence is assumed to indicate an underlying bisexuality of the genetically-determined neuro-muscular constitution in both sexes, although in all cases structural and functional factors impose definite limits upon the completeness of bisexual mating behavior.

5. Behavior involving auto-genital stimulation is common to male and female mammals. In sub-primate species this activity consists chiefly of manipulating and licking the external genitalia during pre- and inter-copulatory intervals; but in the primates manual and oral masturbation occurs in a variety of situations and may continue to the point of orgasm. In observations of this type it is possible to discern a biological or evolutionary basis for certain auto-erotic practices common to human beings.

C. *Hormonal Evidence.* There are several lines of evidence to prove that gonadal hormones exert specific and powerful effects upon sexual behavior in all mammalian forms.

1. In seasonally-breeding species the occurrence of intense and complete sexual performance coincides with periods of maximal secretory function in the testes and ovaries. In year-round breeders the male is continuously active sexually, while the female's periods of receptivity occur when mature follicles are present and the estrogen level is high. The relationship between ovarian condition and sexual behavior is clear-cut in females of lower mammalian species, but the female monkey shows some willingness to receive the male at times when the ovaries do not contain ripe follicles; and even greater emancipation from hormonal control is seen in the mating activity of the female chimpanzee, who

exhibits periodicity of responsiveness but may permit copulation at any stage of the ovarian cycle. The highest degree of freedom from ovarian direction of sex desire obtains in the human female in whom non-hormonal factors exert at least equally important effects. These observations suggest a progressive, phylogenetic decrease in the importance of ovarian secretions to sexual drive in female mammals, and it has been suggested that this change is directly related to the increasing contribution made by higher nervous mechanisms.

2. Removal of the ovaries promptly and permanently abolishes sexual behavior in females of sub-primate species, and administration of ovarian hormones restores normal mating responses. Gonadectomized chimpanzees continue to display some copulatory behavior after operation, although the surviving sexual activity is less frequent and intense than that exhibited by the intact individual during the period of maximal genital swelling. Administration of estrogen to spayed apes occasions sexual swelling and the restitution of full copulatory behavior. Ovariectomized human females may experience a reduction in sexual desire and capacity for complete coital response; but in many cases no post-operative change is noted, and in either event the effects of replacement therapy are not at all predictable. Here again are indications of an evolutionary decrease in the importance of gonadal hormones to feminine receptivity, a change which may be related to progressive increase in the control exerted by the cerebral cortex.

3. Gonadectomy in adult males of sub-primate species results in fairly rapid loss of the more complete forms of copulatory behavior, although in many individuals incomplete coital responses persist indefinitely. In all cases administration of androgen restores normal sexual behavior. Copulation with intromission survives indefinitely in some castrated male chimpanzees, but androgen must be administered if the ejaculatory reaction is to appear. Among castrated humans individual differences are pronounced, but for years after operation many men suffer little reduction in sexual ability. In the male as in the female it appears that advancing phyletic status may be associated with progressive reduction in the importance of gonadal hormones to full sexual performance, and this change is regarded as a function of increase in the reliance of sexual functions upon higher brain centers, particularly the cerebral cortex.

D. *Concluding Comments.* In the course of mammalian evolution several changes in the physiological basis for sexual behavior appear to have taken place. Increase in the size and complexity of the neo-cortex has been accompanied by progressive encephalization of sensory-motor functions including many of those involved in courtship and mating. Concomitantly the subcerebral mechanisms which originally were capable of mediating sexual responses have come to be more and more dependent upon facilitative impulses from functionally associated circuits lying higher in the nervous system. Progressive encephalization of various sexual activities has resulted in increasing variability and modifiability, both of the types of stimuli adequate to elicit sexual activity and of the overt forms of behavior by which sexual excitement may be expressed. Finally, development of increasing dependence upon facilitation from the neo-pallium has

in some measure freed the more primitive sexual mechanisms from strict control by gonadal hormones.

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RECENT ADVANCES IN THE STUDY OF BIOLOGICAL COMPETITION BETWEEN STRUCTURALLY RELATED COMPOUNDS

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During the past few years compounds which are structurally similar to, but biologically antagonistic to metabolically important substances, have been synthesized in the laboratory or found to exist in nature. These agents which act in competition with vitamins, hormones, or other metabolites exhibit their effects by the production of signs of deficiency of the metabolite to which they bear structural resemblance. This situation has excited extensive study not only because of the light such a subtle relationship may throw on the mechanism of biochemical reactions, but also because some investigators have seen in it the possibility of using the findings as tools in pharmacology, biochemistry, or microbiology. Therefore, a review of existing knowledge of the phenomenon of competition between structurally related compounds may be advisable at this time.

Several excellent reviews dealing with this subject have appeared (17, 18, 3, 115, 159, 160) and these have recounted in some detail most of the experimental findings up to the summer of 1945. Therefore, no attempt will be made to reiterate that which has been said several times before. However, new information has come to light in the intervening time, and furthermore, sufficient delineation and integration have occurred to warrant further discussion.

Let us examine a typical case of the competition between a metabolite and its structural analog so that we may have a point of reference in attempting an understanding of the problems. The metabolite thiamine and its structural analog pyrithiamine provide an example in which many of the features common to the phenomenon may be clearly seen. The formulae of this pair of compounds are shown in figure 1. The two differ in that the thiazole ring of the vitamin is replaced by a pyridine ring in the pyrithiamine, that is, a S atom is exchanged for —CH:CH—. Pyrithiamine was first prepared by Tracy and Elderfield (161) in the anticipation that it would have thiamine potency, but in testing for such activity Robbins (121) found that for two species of thiamine-requiring fungi it was harmful rather than beneficial. Woolley and White (116), who were interested in the phenomenon of competition between structurally related compounds, then fed pyrithiamine to mice, and observed that signs characteristic of thiamine deficiency were produced. The deficiency syndrome appeared with greater speed and more pronounced intensity, and sharper definition of the typical manifestations of avitaminosis B_1 than had ever been achieved in mice by mere restriction of thiamine intake. Hyperirritability, unsteady gait, head retraction, convulsions (initiated by twirling the animal while it was held suspended by the tail head downward), prostration, loss of weight and death have been seen frequently in various animals receiving no thiamine in the diet, but usually only a few of these signs may be observed in any one species, and

with mice, usually only the latter two are noted. However, the entire sequence followed the administration of pyrithiamine. The basal diet fed to these animals contained adequate thiamine to maintain health in the absence of the drug, and when a further quantity of the vitamin was added, the action of the drug was prevented. Furthermore, administration of thiamine cured mice which had been affected by pyrithiamine.

Now, the toxicity of pyrithiamine (i.e., its ability to call forth signs of thiamine deficiency) depended on the ratio of pyrithiamine to thiamine in the diet, and not on the absolute amount of the drug. The effects of 100 lethal doses were completely prevented by increasing the thiamine content of the diet 100-fold.

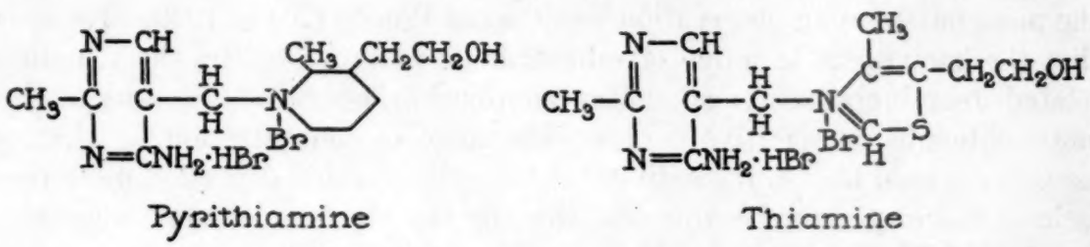

Fig. 1. Structural formulae of thiamine and pyrithiamine

TABLE 1

Response of mice to various doses of thiamine and pyrithiamine

PYRITHIAMINE	THIAMINE	ANIMALS SHOWING DEFICIENCY SIGNS	AVERAGE CHANGE IN WEIGHT
gamma per day	*gamma per day*	*per cent*	*grams per week*
0	1.6	0	+3.0
600	1.6	100	−0.2
300	1.6	100	+1.9
100	1.6	100	+2.5
100	2.0	75	+2.4
50	2.0	0	+3.5
600	61.6	0	+3.1
2,000	60.0	0	+3.6

In other words, pyrithiamine and thiamine competed with each other over a wide range of concentration for the functions of the latter in the mouse, and were thus antagonistic structural analogs. Data to illustrate this point are shown in table 1.

The biological effects of pyrithiamine were not limited to the action on mice, for the drug proved to be capable of inhibiting the growth of a variety of yeasts, molds, and bacteria (117). In preventing the growth of such forms the same type of competition with thiamine was found as had been observed with mice. Since the microbiostasis could be prevented by increasing the thiamine content of the media, the action of the agent could be said to reside in its ability to cause thiamine deficiency of the organisms. In much of the work on the competition between structurally related compounds, bacteria and other microorganisms

have been used as test objects to demonstrate the antagonism. This has been due partly to the fact that such forms make possible more rapid, and usually more quantitative assays than those with laboratory animals. Screening of many substances for a given activity is thus facilitated.

Not all microorganisms were inhibited in growth by pyrithiamine. Only those species which needed thiamine (or its constituent pyrimidine and thiazole parts) as essential growth stimulants were susceptible to its action. The drug was thus a highly selective inhibitor of microbial growth since it distinguished between those organisms which required the vitamin and those which did not.

Competitive relationships between metabolites (vitamins, hormones, and other biologically active compounds) have been observed for many years. Perhaps the most outstanding observation was that of Woods (20) in 1940. He showed that the bacteriostatic action of sulfanilamide was reversed by the structurally related p-aminobenzoic acid. The relationship between the drug and the metabolite was competitive over a wide range of concentration, so that, just as we have seen above, the activity of the sulfanilamide depended more on the ratio of it and p-aminobenzoic acid than on the absolute amount present. At the time of Woods' work, p-aminobenzoic acid was not known to be a metabolite, but he showed that the natural inhibitor of sulfonamide action (which was present in yeast) had properties similar to those of this substance. Shortly after his postulation of the rôle of this compound in metabolism abundant proof was forthcoming from varied sources (162, 163) to substantiate his claim. Not only was p-aminobenzoic acid found in many living cells, but it was shown to be an essential nutrient for some microorganisms, and finally to be an integral part of the vitamin pteroyl glutamic acid (folic acid) (164).

As a result of his observations, Woods proposed the idea that sulfanilamide and its derivatives owed their bacteriostatic action to the competition which existed between them and the metabolite p-aminobenzoic acid. The bacteria were thus effectively deprived of the latter, and in such condition were unable to thrive within the host.

The discovery of the relationship between the sulfonamide drugs and p-aminobenzoic acid was not the first example to be observed of competition between structurally similar compounds, but it was one of the most important because it offered an explanation for the mode of action of a set of new and dramatic therapeutic agents. The practical importance of the drugs was sufficient to stimulate interest in the further investigation of a phenomenon (i.e., that of competition) which previously had been noted incidentally and somewhat casually (3, 115).

In looking back over the literature one frequently finds experimental observations which were baffling to their discoverers, and uncongenial to the modes of biochemical thought at the time, but which now seem understandable, or at least reconcilable in terms of the present knowledge of antagonism between structurally similar compounds. One interesting example of this is the claim of Kuhn (42) that the sex hormone of certain algae was not a single compound, but rather a manifestation of a ratio between two structurally allied carotenoids,

cis- and *trans*-dimethyl crocetin. Sex was determined by the ratio between these analogs. Specific biological effects had been attributed so universally to single and distinct chemical substances that even in 1940 when these results with algae were summarized they sounded somewhat heretical. Some investigators have come to feel now, however, in view of the demonstrable competition between androgen and estrogen in higher animals, and the undoubted structural similarity and coexistence of these hormones in nature, that sex even in higher animals may in part be an expression of competition between related structures (115).

Since 1940, antagonistic analogs have been sought with such industry that there is at least one for each of the water-soluble vitamins, and for two of the four fat-soluble ones, and for certain hormones, amino acids, porphyrins, and purines. Usually for each of these metabolites there is not one but several types of inhibitor, differing qualitatively in their biological effects. Because most of these cases have been reviewed adequately elsewhere (17, 18, 3, 115, 159, 160) nothing will be gained by reiteration. Nevertheless, for purposes of reference and of orientation Table 2 has been compiled to show which metabolites have been converted into antagonistic compounds by alteration of their structures, and the types of change which have been found effective. The table includes information published since the last review of the subject as well as the older examples.

General Considerations. (*a*) *Concerning reversal.* The surest indication that the antagonistic effects produced by a structural analog are due to the competition of that analog with its related metabolite is the ability of the latter to reverse the action of the agent. The evidence is strongest when over a considerable range of concentrations a constant ratio exists between the amounts of the two related compounds which just counterbalance each other. This ratio which is known as the inhibition index (117) is a constant for many of the cases listed in table 2. It is so, for example, with the sulfonamide drugs and p-aminobenzoic acid, and with pyrithiamine and thiamine. However, it does not hold universally. The situation with 3,3′-methylenebis-(4-hydroxy-coumarin) and vitamin K will serve to illustrate this point. With this pair of compounds it is possible to demonstrate (142, 165) that the pharmacological action of the former in bringing about the signs of vitamin K deficiency is reversed by sufficient amounts of the latter, but this is only true over a restricted range of concentration of the drug. As the quantity of the drug is increased, a point is soon reached beyond which it is not possible to achieve such reversal. Furthermore, there is no evidence to show that the inhibition index (117) is a constant even over the limited range where reversal can be demonstrated.

An additional obscurity in this case is the fact that very large amounts of vitamin K are required to antagonize the action of the drug. About 25 mgm. of the vitamin must be used to erase the effects of 10 mgm. of the drug in a rat. This means that the inhibition index is less than 1. For most inhibitor-metabolite pairs the index is much greater than 1.

Another example of this atypical behavior is to be found with 2,3-dichloro-

TABLE 2

Metabolites and structural analogs which have been found antagonistic to them

METABOLITE	ANALOG	STRUCTURAL ALTERATION	BIOLOGICAL SYSTEM AFFECTED	REFERENCES
Acetic acid	Fluoro-acetic aid	F for H	Acetate oxidase	158
Adenine	Benzmidazole and derivatives	2 C for 2 N; side chain alterations	Microorganisms, animals	1, 2, 3
	Triazolopyrimidines	N for C	Microorganisms	4
β-Alanine	β-Amino-butyric acid	CH_3 for H	Yeast	5
	Propionic acid	H for NH_2	Bacteria	157
	Asparagine	COOH for H; $CONH_2$ for COOH	Yeast	6
α-Alanine	Glycine	H for CH_3	Bacteria	7
Amino acids	α-Amino-sulfonic acids	SO_3H for COOH	Bacteria	8, 9
	Other amino acids		Bacteria	10, 7, 11
Aspartic acid	Hydroxy-aspartic acid	OH for H	Bacteria	12
Ascorbic acid	Glucoascorbic acid	Addition of CHOH and optical inversion	Animals; liver enzymes	13, 14, 15
p-Aminobenzoic acid	Sulfanilamide and derivatives	SO_2NH_2 or derivative for COOH	Microorganisms	16, 17, 18, 19, 20, 32
	p-Amino benzamide	$CONH_2$ for COOH	Bacteria	21, 22
	Carbarsone and related arsenicals	As for C in a COOH group; derivatives of this	Microorganisms, animals	21, 23, 24, 25, 26, 27, 28
	Phosphanilic acid	PO_3H_2 for COOH	Microorganisms	155
	Heterocyclic acids, e.g., 6-amino-nicotinic acid	N or S for C	Bacteria	29
	Ring-substituted PAB	Halogen or alkyl for H	Bacteria	30, 29, 31
	p-Amino-acetophenone and derivatives	COR for COOH	Bacteria	22, 33
	p-Nitrobenzoic acid	NO_2 for NH_2	Bacteria	154
Biotin	Desthiobiotin and derivatives	2 H for S	Microorganisms	34, 35, 36, 37
	Biotin sulfone	SO_2 for S	Microorganisms	35
	Ureylenecyclohexyl aliphatic acids	2 C for S; and derivatives with shorter side chains	Microorganisms	39, 40
	Desthioisobiotin	Loss of S, geometric isomerism	Insects	78
Choline	Triethyl choline	3 ethyls for 3 methyls	Frog muscle, mice	41
Cocarboxylase	Thiamine-thiazole pyrophosphate	Loss of pyrimidine portion	Carboxylase	125
Cis- or *trans-*crocetin dimethyl ester	*Trans-* or *cis-*crocetin dimethyl ester	Geometric isomerism	Algae	42
Folic acid	See Pteroyl glutamic acid			
Glutamic acid	Methionine sulfoxide	$SOCH_3$ for COOH	Bacteria	43, 44
Guanine	Triazolopyrimidines	N for C	Bacteria	4
	Benzimidazole	2 C for N	Microorganisms	2
Histamine	Imidazole and derivatives	Elimination or substitution of part of the molecule	Smooth muscle, histamine shock in animals	17, 45, 46, 47, 48, 49, 50, 51, 52

TABLE 2—*Continued*

METABOLITE	ANALOG	STRUCTURAL ALTERATION	BIOLOGICAL SYSTEM AFFECTED	REFERENCES
Hypoxanthine	Hydroxy-triazolo-pyrimidine	N for C	Bacteria	4
Indoleacetic acid	Phenyl butyric acid	Elimination of N and shift of one C	Plants	53
Inositol	Hexachlorocyclohexane	6 Cl for 6 OH	Yeast	54
Isoleucine	Leucine	Position isomerism of one CH_3	Bacteria	55
Isoleucine + valine	Phenyl alanine or nor-leucine or nor-valine	C_6H_5 for alkyl position isomerism	Fungi	56
Leucine	d-Leucine	Optical inversion	Bacteria	57
Lysine	Arginine	Guanidino for amino, elimination of CH_2	Fungi	58
Methionine	Methoxinine	O for S	Bacteria	4
	Ethionine	CH_3 for H	Bacteria, animals	59, 60
Nicotinic acid (or amide)	Pyridine-3-sulfonic acid (or amide)	SO_3H for COOH	Microorganisms, animals	61, 62, 63, 64, 65, 66, 67
	3-acetyl-pyridine	$COCH_3$ for COOH	Animals, not in microorganisms	33, 68
	5-thiazole carboxamide	S for CH=CH	Certain bacteria	65, 69
Pantothenic acid	Thiopanic acid (pantoyl taurine) and derivatives	SO_3H and derivatives for COOH	Microorganisms, pantothenate utilizing enzymes, not animals	70, 71, 72, 67, 73, 74, 75, 76, 77, 79, 80, 81, 82, 83, 6, 85, 86, 92, 93
	Pantothenyl alcohol	CH_2OH for COOH	Microorganisms, not animals	84, 87
	α- or β-Methyl pantothenic acid	CH_3 for H	Microorganisms	88, 89, 202
	Substituted panto-amides other than the above	Alkyl or OH- and NH_2-alkyl for CH_2CH_2COOH	Microorganisms	90, 91
	Phenyl pantothenone	COC_6H_5 for COOH	Microorganisms	94, 95, 3, 96
	Salicylyl β-alanine	o-hydroxy-benzoyl for pantoyl	Microorganisms	97
	γ′-Methyl pantothenic acid	CH_3 for H	Bacteria	156
Phenyl alanine	β-Hydroxyphenyl alanine	OH for H	Bacteria	98
	Thienyl-alanine	S for CH=CH	Microorganisms	99, 98, 100
Porphyrins such as hematin and protoporphyrin	Porphyrins lacking vinyl groups		Bacteria	101
Pteroylglutamic acid	Pteroyl-triglutamic acid	Addition of two glutamic acids	Transplanted tumors	102
	Xanthopterin	Loss of p-amino-benzoyl glutamic acid	Transplanted tumors	102
Pyridoxine	Desoxypyridoxine	H for OH	Chickens	103
Riboflavin	6,7-dichloro-riboflavin	2 Cl for 2 CH_3	Microorganisms	104
	Isoriboflavin	Shift in position of CH_3	Animals, not bacteria	105, 110
	Corresponding phenazine	2 C for 2 N, 2 NH_2 for 2 OH	Microorganisms, animals	106, 109
	Galactoflavin	Dulcityl for ribityl	Animals	107
	Lumiflavin	CH_3 for ribityl	Bacteria	108, 109, 204
	Araboflavin	Inversion of position of OH	Animals	203

TABLE 2—*Concluded*

METABOLITE	ANALOG	STRUCTURAL ALTERATION	BIOLOGICAL SYSTEM AFFECTED	REFERENCES
Succinic acid	Malonic acid	Loss of CH_2	Succinic oxidase	111
	Sulfonated succinic acid	SO_3H for H	Succinic oxidase	112
Testosterone	Estradiol	Benzene ring for cyclohexane ring	Animals	113, 114, 115
Thiamine	Pyrithiamine	CH=CH for S	Animals, microorganisms	116, 117, 118, 119, 120, 121, 201
	Oxythiamine	OH for NH_2	Animals, fish thiaminase	122
	Butyl thiamine	Butyl for CH_3	Animals	123
	Aminobenzylmethyl-thiazolium chloride	2 C for 2 N, loss of side chains	Fish thiaminase	124
Thymine	5-substituted pyrimidines	OH or NO_2 or Br for CH_3	Bacteria	126
α-Tocopherol	α-Tocopherol quinone	Opening of ring by addition of H_2O	Animals	127
Thyroxine	Ethers of diiodotyrosine	p-nitro-benzyl or p-nitro-phenylethyl or benzyl for p-hydroxy-diiodophenyl	Tadpoles	128
Tryptophane	Indoleacrylic acid	Loss of NH_2	Bacteria	129
	Naphthylacrylic acid	Loss of NH_2, C=C for N	Bacteria	130
	Styrylacetic acid	Loss of NH_2, substitution of aliphatic unsaturated side chain for pyrrol ring	Bacteria	130
	5-methyl-tryptophane	CH_3 for H	Bacteria	131
Uracil	Barbituric acid	OH for H	Bacteria	132
	Thiouracil	S for O	Bacteria	133
Vitamin K	Dicoumarol and derivatives	O for C, side chain alterations	Animals	134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148
	Iodinin	2 N for 2 C, side chain alterations	Bacteria	149
	α-Tocopherol quinone	2 CH_3 for benzene ring	Animals	127
	2,3-dichloronaphthoquinone	2 Cl for alkyl side chain	Microorganisms	150, 151
	2-substituted-3-hydroxy-naphthoquinones	OH for H, change in alkyl substituent	Animals, not bacteria	152, 153

naphthoquinone and the structurally similar vitamin K. Here, too, competition can be demonstrated over only a narrow range of concentration and with only certain species (151). A plausible explanation of this case was given by the finding that the vitamin itself was harmful in large doses (151). However, there are examples of the failure to demonstrate typical competition where this explanation of toxicity of the metabolite cannot be applied.

Why, then, are such cases included in a discussion of competition between structurally related compounds? In the first place, several of these questionable

analogs call forth in animals many of the signs characteristically associated with a deficiency of the metabolite to which the drug is structurally related. For example, 3,3′-methylenebis-(4-hydroxy-coumarin) brings about subcutaneous hemorrhages, and prolonged blood clotting-time attributable to decrease in the plasma prothrombin. These are typical manifestations of avitaminosis K. Again, α-tocopherol quinone causes pregnant mice to fail to produce young in a manner similar to that seen in tocopherol deficiency (127). Hence, despite the failure to reverse these effects with the vitamin there is some reason to relate the action of the drug to an interference with the biological action of the metabolite. However, in the cases of mere inhibition of microbial growth by an analog of a metabolite, the response (i.e., inhibition of growth) is too nonspecific to link the action of the drug with that of the metabolite unless reversal of the effect of the former by the latter can be demonstrated.

In the second place, the ability to demonstrate competitive reversal frequently depends on the selection of the proper species or biological system. Take for example the classical case of the sulfonamide drugs and p-aminobenzoic acid. Although the competition of these substances in producing bacteriostasis has been demonstrated abundantly with a wide variety of species, Tamura (166) has shown that no reversal of sulfonamide action occurred with *B. tularensis*. Again, Woolley and Collyer found (94) that phenyl pantothenone prevented the growth of all microbial species examined, but that reversal of this effect could be achieved with the related metabolite pantothenic acid only in those forms which were stimulated to grow by the vitamin. With the non-pantothenic acid-requiring microorganisms the vitamin was unable to reverse the inhibition of growth. If only organisms not requiring the vitamin had been examined, what would have been concluded about the action of the drug?

In view of these aspects, it seems that while reversal of the action of a structural analog by increased amounts of the metabolite is the acid test, it is not an entirely sufficient one. In deciding which cases shall be accepted to membership in the phenomenon of competitive inhibition, and which shall be excluded, no single criterion will suffice. Just as with the definition of enzyme action (115), here, too, one must content himself with descriptions of features common to many individual cases but not necessarily shared by all. Nature is not a series of discrete quanta of phenomena, but rather a continuous gradation of them.

(*b*) *Dependence of antagonistic action on nutritional requirement.* Frequently an analog is found to be antagonistic to a metabolite only if the latter is a nutritional requirement of the organism with which the test is being conducted. For species which do not need the metabolite in their food, and can synthesize it themselves, the analog has no detectable effect. Thus thiopanic acid affects only certain bacteria which will not grow without pantothenic acid, and pyrithiamine retards the growth of microorganisms only if they demand an exogenous supply of thiamine or its constituent thiazole and pyrimidine parts (117). Many exceptions to this generalization are known. For example, the sulfonamide drugs, phenyl pantothenone and its derivatives, benzimidazole and its derivatives, and 2,3-dichloronaphthoquinone act against organisms irrespective

of their nutritional requirements for the related metabolites. Some antagonists, such as phenyl pantothenone or glucoascorbic acid (13, 14), exhibit properties midway between these extremes, for although they affect organisms without regard to nutritional requirements, their action is reversed by the related metabolite only when the particular organism needs the latter as a growth factor. The case of phenyl pantothenone was mentioned in this respect in section (*a*) above. That of glucoascorbic acid will illustrate a similar phenomenon in the animal kingdom. This substance produced a disease resembling scurvy in both mice and guinea pigs, but the condition was prevented by ascorbic acid only in the latter, or ascorbic acid-requiring, species, and not in the former, or vitamin C-synthesizing animals.

The explanation of the dependence of effect on nutritional requirement may be different for the several inhibitor-metabolite pairs for which it has been observed, but at least in the case of pyrithiamine the mechanism has been elucidated (118). Those forms which do not require thiamine, and which are able to thrive in the presence of the drug, possessed a system, presumably enzymic, which split the drug into its pyrimidine and pyridine parts in the same fashion as thiamine may be cleaved at an analogous point into its pyrimidine and thiazole halves. Organisms which could not synthesize thiamine did not possess this ability to destroy the agent, at least not in appreciable amount, and hence were subject to attack.

Another insight into the relationship between nutritional requirement and effectiveness of an agent may be had in the case of organisms which need folic acid. Most such species are rather resistant to the bacteriostasis exerted by sulfonamides. Now, p-aminobenzoic acid is a part of folic acid, and presumably is used to form the vitamin. If the sulfonamides compete with p-aminobenzoic acid in this synthesis, organisms which cannot perform the reaction anyway, and must depend on the medium for their folic acid, would be expected to be less affected by sulfonamides. Although such a correlation between folic acid requirement and sulfonamide resistance actually does exist (167), it is probably only one aspect of susceptibility to these drugs.

(*c*) *Spectrum of antagonistic action of analogs.* Gradations of activity ranging from full vitamin potency to strong antagonism may be observed if several compounds and organisms are examined. This fact must be borne in mind in the formation of any hypothesis for the mode of operation of antagonistic structural analogs. As one examines the data available at present he can see three aspects of this situation. First, a single inhibitory structural analog may either be antagonistic or have weak metabolite activity when tested on the same organism. Which one of the two opposing effects is manifested is determined by the concentration of the agent. For example, Pollack (88) found that α-methyl pantothenic acid would inhibit growth of *L. casei*, but that as the concentration was raised a stimulation of growth similar to that caused by panthothenic acid was produced. Shive and Snell (90) confirmed this finding, and observed similar situations with certain other inhibitory structural analogs of panthothenic acid. The slight vitamin potency of the analogs, weak as it was, was sufficient to prevent the achievement of complete bacteriostasis because

at the high levels of agent which would have been necessary to bring this about, the pantothenic acid activity of the compound made itself felt. Kuhn *et al.* (22) similarly found both inhibitory and stimulatory actions of p-aminobenzamide on bacteria. Likewise, Woolley (128) observed that the p-nitrobenzyl ether of N-acetyl diiodotyrosine not only was an antagonist of thyroxine as measured on tadpoles, but also in the absence of the latter compound, it was weakly active as the hormone. Just as in the previous example, this metabolite activity of the analog at high concentrations limited the realization of total antagonism of the hormone.

Secondly, in a homologous series of compounds, some may show positive metabolite activity and others may be antagonistic. A good illustration of this is found with derivatives of thiamine which differ in the nature of the alkyl side chain at position 2 in the pyrimidine ring. The vitamin has a methyl group at this point, and, of course, has full metabolite potency. The ethyl has less, but still some vitamin activity. However, the butyl compound competes with thiamine for functions of the latter in rats (123). In this example, the shift from metabolite to anti-metabolite activity is more striking than in the usual cases because with changing structure there is a gradual progression from full to partial activity, and then to antagonistic potency.

Thirdly, a single analog may be active in some species as the metabolite, and in others it may be antagonistic. For example, desthiobiotin is able to replace biotin in promoting growth of *Saccharomyces cerevisiae*, but acts in competition with the vitamin in the growth of *Lactobacillus casei* (34, 35, 36). Why this should be so has been explained by Dittmer and du Vigneaud (35) who showed that the yeast converted desthiobiotin to biotin by the insertion of a S atom, while the lactobacillus could not do this. If the former organism had been unable to effect the conversion it might have succumbed to the antagonistic effects of the analog just as did the bacterium. In similar vein, Woolley (118) has shown that when *Endomyces vernalis* was made resistant to pyrithiamine by continued culture in the presence of the drug, it acquired the power to use pyrithiamine in place of thiamine at the same time that it became insusceptible to the inhibitory action of the analog. As was discussed above, resistance was acquired by development of the ability to split pyrithiamine into its pyrimidine and pyridine halves. Since the pyrimidine was the same as that in thiamine, and since for *Endomyces* this fragment possessed full vitamin activity, the organism used it as a growth factor. Similarly, although desoxypyridoxin was a powerful competitor to pyridoxin in the chick (103) it possessed no activity for the rat[1], and for lactic acid bacteria it had weak vitamin potency (168).

The mere ability of some organisms to convert an antagonistic analog into the metabolite as in the examples given above, is not the sole explanation of the varied susceptibility of species. For example, when the S atom of biotin was replaced by an O, the resulting analog, oxybiotin, was found to have vitamin activity equal to that of biotin for some organisms (169), slight potency for others (170), and none at all for still others (171). Indeed, it was actually

[1] Recently some antipyridoxin activity of this compound in rats has been demonstrated. (Porter, C. C., I. Clark and R. H. Silber, J. Biol. Chem. **167**: 573, 1947).

toxic for certain forms although this toxicity was not demonstrated to be due to competition with biotin. However, no conversion of oxybiotin to biotin could be shown in those microorganisms which used it in place of the naturally occurring vitamin (172). Again, the ethyl analog of pyridoxin (2-ethyl-3-hydroxy-4,5 dimethylol-pyridine) was found to replace the vitamin for tomato roots (173) but to be an anti-pyridoxin in certain fungi (174). It is unlikely that the tomato roots utilized the compound by exchanging the ethyl for a methyl group.

Finally, the ultimate example is provided by the work of Emerson (175) who showed that by long continued cultivation of a *Neurospora* in the presence of sulfanilamide, a strain was secured for which sulfanilamide was a nutritive essential, and p-aminobenzoic acid was an inhibitor of growth. In the parent strain the reverse situation obtained since the sulfonamide was the toxic compound.

(*d*) *Hypotheses concerning mechanism.* Of the various hypotheses proposed to explain why structurally similar compounds should compete with each other in biological systems, the one which fits the observed facts best and which has been most stimulating to further discovery is the one which pictures metabolite and inhibitory analog contending for the specific part of a protein, possibly an enzyme, with which the metabolite normally reacts. Some facts observed experimentally require modifying assumptions in order to conform to this view. One such fact is that subinhibitory concentrations of antagonists such as sulfanilamide or pyrithiamine (117, 115) frequently cause stimulation rather than inhibition so that it is necessary to assume compensatory mechanisms at work in the cell in order to reconcile the observation with the hypothesis. However, when one views the large body of evidence which is best explained by this view of mechanism, and recalls how productive it has been of new findings, he is persuaded that until a better working hypothesis comes along he will hold this one as true. This is especially so when one remembers that rival explanations such as the one that metabolite inhibitors exert a narcotic effect (176) have been rather sterile. Let us then examine the favored hypothesis.

According to this view, a metabolite functions by first combining with a particular cellular unit which is usually regarded as an enzyme or possibly some other specific protein. The union of a substrate with its enzyme would be an analogous reaction, and indeed, the metabolite in this rôle should be regarded as a substrate. The combination then proceeds to pass through a second metabolic reaction or a chain of reactions with a new compound (or substrate) which is transformed and the metabolite is either regenerated or changed into another substance. The cycle of alterations undergone by cozymase in transporting hydrogen would be an example of such a process. Now, in order for the first step to occur, the metabolite must possess certain structural features, and the firmness of combination with the protein is determined in part by these. A similarly constituted compound is able to undergo this combination, but since its structure is not identical with that of the metabolite, its firmness of union will be different. The conjugate of analog and protein is, however, a new and foreign compound

and is unable to proceed through the rest of the cycle of reactions. Like the fabled dog in the manger the analog denies the organism the use of the metabolite and thus creates a deficiency of the latter.

The union of metabolite and protein or of analog and protein is a reversible one usually, so that relative concentrations and relative combining power of metabolite and analog determine which one shall enjoy the protein. Since the metabolite usually has the greater combining power, less of it than of analog will saturate the protein. Therefore, as was pointed out before, the inhibition index is generally greater than 1. As the concentration of analog is increased in the presence of a constant amount of metabolite, a point is reached at which the protein unites with the former rather than with the latter substance, and inhibition of the metabolic function results. If the amount of metabolite is then raised, the analog is dislodged and normal function is resumed. If an analog should be so constituted that it would combine irreversibly with the protein, an inhibitor would result which would call forth signs of deficiency in the organism but these manifestations could not be reversed by increased doses of the metabolite.

What are the concrete pieces of evidence for this hypothesis? The major ones are the following. In the first place, it is fairly well established by numerous studies in enzymology that substrate and enzyme actually do combine reversibly as the first stage in the reaction. Here then is one type of system in which the first reaction in our hypothesis does occur. Indeed, such combinations are known which involve classical metabolites, e.g., the attachment of thiamine pyrophosphate to carboxylase. Furthermore, the competition of structurally similar substrates for a single enzyme has been known for decades, and can be seen to good advantage in the contending of succinate and malonate for succinic dehydrogenase (111). Finally, in non-enzymic reactions between specific proteins and metabolites, solid proof exists that the metabolite can be displaced from the combination by structurally analogous compounds. The best known case is that of the displacement of oxygen in oxyhemoglobin by carbon monoxide. If there are 210 molecules of oxygen for each one of carbon monoxide, the latter is excluded from half the protein and an equal mixture of oxyhemoglobin and carbon monoxyhemoglobin exists. As the relative concentration of carbon monoxide is increased, oxygen is pushed from its combination and carbon monoxide takes its place. As the relative concentration of oxygen increases, the reverse process occurs. Again, biotin combines in molecular proportions with a specific protein, antibiotin or avidin (117, 178). When biotin sulfone is admitted to this system containing the combination, biotin is displaced and appears free in the solution (35). Biotin sulfone not only competes with biotin in this simple system but also functions antagonistically with it in the growth of *Saccharomyces cereviseae*. Another example is the appearance of acetyl choline in solution when sufficient physostigmine is added to a preparation containing cholinesterase and the hormone (179). Thus there is a considerable body of evidence to show that metabolites can be displaced from combination with specific proteins by adequate amounts of certain structural analogs.

Whether they all can be, or whether in fact they all act by combination with proteins or other cell structures, cannot be said at present.

Although many authors have made the tacit assumption that analogs compete with metabolites acting as co-enzymes, there is no direct evidence that they do. In fact, most available data show that the competition is expressed when the metabolite acts as a substrate and not as a co-enzyme. In behaving as a substrate, the metabolite is either degraded or is synthesized into a more complex molecule. This latter compound may then proceed to function as a co-enzyme. For example, pyrithiamine does not compete with thiamine pyrophosphate in the rôle of co-carboxylase. Rather it is probable that the competition between thiamine and pyrithiamine occurs in the synthesis of the co-enzyme from the vitamin.

Intensive study of the mode of action of several inhibitory structural analogs has indicated that it is usually a synthetic or anabolic reaction rather than a degradative or catabolic one which is affected. However, sufficient numbers of cases have not been examined intensively enough to allow one to conclude that this is a general situation. Indeed, the competition between succinate and malonate, or that between thiamine and o-aminobenzyl methyl thiazolium chloride (124) are examples of the participation of inhibitory analogs in degradative reactions. Nevertheless, some insight has been gained into synthetical processes by studies of antagonism, and therefore this aspect of the mechanism of action deserves our attention.

Pantoyl taurine or thiopanic acid is a bacteriostatic analog of pantothenic acid. McIlwain (82) has shown that this agent competes with the vitamin in resting streptococci in an enzymic process concerned with the conjugation of pantothenic acid into a larger molecule in the cells. Although the nature of this conjugate is unknown, good evidence exists for its occurrence in bacteria as well as in animals (180). Therefore, pantoyl taurine competes with pantothenic acid as a substrate used in the synthesis of a larger, and presumably metabolically important, substance.

Again, Lampen and Jones (167) have produced strong evidence that the sulfonamide drugs compete with p-aminobenzoic acid as substrate for the synthesis of pteroyl glutamic acid, a metabolically important conjugate of p-aminobenzoic acid. As was discussed in a previous section, these investigators found that those bacteria which require pteroyl glutamic acid as a nutritive essential, and hence cannot synthesize it, are not susceptible to bacteriostasis by concentrations of sulfonamides which affect other bacteria. Presumably, if the organism does not possess a means of synthesizing PGA, it cannot be harmed by an agent which acts to inhibit this synthesis. Furthermore, PGA antagonises the bacteriostatic action of sulfonamides on certain susceptible species. In other words, when the synthesis of PGA is inhibited, the harm to the organism can be circumvented by supplying in the medium the product of the reaction, viz., PGA. They showed as further evidence that while the antagonism between p-aminobenzoic acid and the sulfonamide is of a competitive nature over a wide range of concentration, the same amount of PGA is required to reverse a large dose of the

sulfonamide as is needed for a small one, i.e., that the antagonism is not competitive. (See Table 3.) Prior to the discovery of p-aminobenzoic acid as a part of PGA, Miller (181) had shown that when bacteria were grown in the presence of sulfonamides, the amount of PGA which they formed was markedly reduced. In the light of all this evidence, the most plausible explanation for the bacteriostasis caused by sulfonamides is that they compete with p-aminobenzoic acid for the synthesis of pteroyl glutamic acid (folic acid). Since some animals need the latter, they are like the PGA-requiring bacteria in that they do not possess the metabolic process with which the sulfonamides interfere.

This hypothesis about mechanism, which may be called the displacement hypothesis, has its roots extended far back into biochemistry and pharmacology. In various forms it has been reiterated since the days of Ehrlich. The competition of structurally similar substrates for specific enzymes reaches back

TABLE 3

*Data of Lampen and Jones showing the growth and antisulfonamide activity of pteroylglutamic acid and p-aminobenzoic acid**

COMPOUND	S. FAECALIS (RALSTON) Half maximum antagonism of sulfadiazine (SD)				50 PER CENT INCREASE IN TURBIDITY	S. FAECALIS R, HALF MAXIMUM GROWTH
	1 γ SD per ml.	10 γ SD per ml.	100 γ SD per ml.	1000 γ SD per ml.		
p-Aminobenzoic acid	0.003	0.03	0.3	3.0	0.001	Inactive
p-Aminobenzoylglutamic acid	1.	30	300	>300	0.05	Inactive
Pteroylglutamic acid	0.0003	0.0003		0.0003	0.0001	0.00015
Pteroyltriglutamic acid	0.004	0.004	0.004	0.008	0.008	0.003
Thymine	0.06	0.25	0.25	0.25	0.25	0.3–0.5

* All values are given in micrograms per ml., after 24 hours' incubation.

through the work of Quastel and Wooldridge with succinic dehydrogenase in 1927, at least to 1910 when the inhibition of amylase by various carbohydrates was studied by Wohl and Glimm (182). Many of the current ideas especially as they apply to pharmacology were clearly stated by Clarke in 1937 (183). Woods (20) and Fildes (184), and the contemporary reviewers and investigators have discussed and added to it. It is a concept which has grown with the acquisition of biochemical knowledge.

(*e*) *Competition between structurally dissimilar compounds.* The action of certain agents is antagonized not only by the metabolites to which they bear analogy, but also by structurally unrelated substances. If the subject of mere antagonism of biochemical reactions was to be discussed fully it would take us far afield from the purpose of this review which is to describe the antagonism between structurally similar materials. As others have pointed out (183, 17) two compounds may be antagonistic because they react with each other to form precipitates or biologically inert substances, or because one injures the living

cell in such a way that the other is able to replace the lost function. Now surely the antagonism between the sulfonamides and pteroyl glutamic acid which was discussed above is of this latter variety, and yet it impinges so directly on the phenomenon of competitive antagonism between structural analogs that it must be touched upon here. By the same token we must consider a few more examples but leave to others the treatment of such agents as thiouracil which antagonizes thyroxine by inhibiting its formation. Once again the problem of where to set the limits of a biological phenomenon is plagued by the continuity and interrelationships of nature.

Not only can the growth-inhibiting properties of sulfanilamide be overcome with p-aminobenzoic acid, but they may also be counteracted with methionine or with adenine (60, 185, 186, 205). However, while the action of increasing concentrations of the sulfonamide is negated by proportional increases of p-aminobenzoic acid so that the inhibition index remains constant, this is not true of antagonism between sulfanilamide and either methionine or adenine. With these latter substances as the concentration of drug is increased a point is soon reached beyond which no amount of material will effect reversal. Furthermore, the concentration of adenine or methionine needed to counteract a given quantity of sulfanilamide is far greater than that of p-aminobenzoic acid. Consideration of these facts led Harris and Kohn (60) to postulate that methionine or adenine might be products of a metabolic reaction for which p-aminobenzoic acid was required. This same idea was adopted by Shive and Roberts (186) who elaborated it with a mathematical treatment. Para-aminobenzoic acid was pictured as participating in several biochemical transformations, the product of one being adenine and of another methionine. Some supporting evidence for this postulate was cited, but hypothesis is still ahead of proof.

Other cases of antagonism between structurally dissimilar compounds are known. Thus the microbiostatic effects of phenyl pantothenone are prevented by glutamic acid, proline, or histidine as well as by the structurally related pantothenic acid (95), and the pharmacological manifestations of 3-acetylpyridine in mice are reversed by tryptophane as well as by the analogous nicotinic acid (187). The general features of the antagonism between the unrelated compounds in these cases are similar to those discussed for the sulfonamides and methionine and adenine. Curiously enough, the heterologous reversing agents in most instances are amino acids (3).

For many inhibitory structural analogs there are species in which the related metabolite will not compete with the agent (see section (*a*) above). However, in such organisms the structurally dissimilar reversing agent frequently will counteract the manifestations. For example, although pantothenic acid was unable to reverse the inhibition of growth of *Saccharomyces cereviseae* produced by phenyl pantothenone, glutamic acid, proline, or histidine would do it. Again, while p-aminobenzoic acid was unable to counteract p-aminomethylbenzene sulfonamide (marfanil), methionine was capable of reversing it. From these and similar examples it would seem that the heterologous naturally occurring

reversing agents (metabolites) may be more universally effective than the analogous ones.

Competition between Structurally Analogous Drugs. It is not necessary that one of a pair of antagonistic structural analogs be a metabolite in order that biological competition may be manifested. Two substances entirely foreign to an organism may be shown to contend within it in order to exert a pharmacological action. Thus, some of the effects of morphine in dogs and mice were counteracted by the structurally related allyl normorphine (188). It is relatively certain that neither of these substances occurred in these animals. In view of this situation, the competition in yeast between 2,3-dichloronaphthoquinone and vitamin K may be regarded as the contention of two foreign substances, since vitamin K has not been detected in this organism (151). However, on the other hand, if vitamin K were an important substance to the yeast cell and yet occurred as only a few molecules per cell, its presence could not be detected by present methods. Whether or not structurally similar drugs compete with each other, because they both are analogs of some normal metabolite cannot be decided from existing knowledge.

Applications to Pharmacology. Because the phenomenon of competition between analogous compounds offered a plausible explanation of the mode of action of the sulfonamide drugs, the expectation arose that new agents for combatting infectious diseases might be formed by suitably altering the structures of other metabolites (184, 189, 160). Since initial attempts to do this met with scant success, several students of chemotherapy of infectious diseases were led to doubt the feasibility of such an approach. Nevertheless progress is being made so that there is still reason to cherish the original ideas. For example, 2,3-dichloronaphthoquinone, a useful agent in the chemotherapy of fungal infestations of plant materials (150), was developed empirically, and then shown to compete with vitamin K (151). The sequence of events in this case paralleled those with sulfanilamide and p-aminobenzoic acid. In similar fashion, Kirkwood and Phillips (54) have indicated that the insecticide hexachlorocyclohexane, owes part of its pharmacological action to the fact that it is an analog of inositol, because the vitamin will reverse the yeast-growth-inhibiting powers of the drug. Here again the usefulness of the agent was established before its relationship to a metabolite was pointed out.

Let us now see whether the converse is true; namely, that active drugs can be produced by intentionally modifying some metabolite. McIlwain and Hawking (73) demonstrated that pantoyl taurine, or thiopanic acid, an inhibitory analog of pantothenic acid, could protect rats from a fatal infection by streptococci, but this agent was too weakly active to make it of any value as a practical drug, and the same proved to be true of several derivatives of it. Finally, however, White *et al.* (93, 17) found that the dibromoanilide of thiopanic acid was a rather potent chemotherapeutic agent in animals. Furthermore, phenyl pantothenone, another type of pantothenic acid analog, has proven to be as effective as quinine in the treatment of blood-induced malaria of birds, and likewise to be of value in similarly initiated infestations of man (3, 96). Trial

of phenyl pantothenone in malaria was prompted by Trager's observation (190) that pantothenic acid increased the survival time of the parasites *in vitro*, and hence was probably of importance in their economy. These small advances therefore may serve as straws in the wind to point the direction of future studies. Empiricism will undoubtedly lead to many discoveries in this field, just as it has always done, but a rational approach is commanding some attention.

In pursuing this rational approach, one guidepost must be the selectivity of action of the agents. If an inhibitor is very effective in causing signs of deficiency of the host, its usefulness in combatting a parasite will be small even though it may be quite potent as a growth-suppressant for the latter. Now, several inhibitory structural analogs of metabolites are known which act against certain classes of organisms and not against others. For example, as we have seen earlier, pyrithiamine affects only those species which have a nutritional requirement for thiamine. The sulfonamides affect many microorganisms but do not produce signs of deficiency of p-aminobenzoic acid when given in therapeutic amounts to animals, and there is some evidence that this selectivity is related to the ability to synthesize pteroyl glutamic acid (see above). Phenyl pantothenone, as well as other known antagonists of pantothenic acid, does not cause signs of deprivation of the vitamin in animals, although it is quite active against microorganisms. Acetylpyridine competes with nicotinic acid in animals, but not in bacteria or yeasts (68), and 2,3-dichloronaphthoquinone is far more toxic to fungi and yeasts than to bacteria and animals (151). Although some insight has been gained into the reasons for such discrimination, very little is known about the matter, and if more were understood, therapeutic agents against infectious diseases might be sought more intelligently.

Woolley (189, 159) has underscored the fact that chemotherapy of infectious diseases is only a small part of the chemotherapy of disease, and has shown how inhibitory structural analogs of metabolites may be applied in attempts to treat non-infectious maladies. It must be emphasized that no practically useful drugs have been turned up as a result of these studies, but some experimental models have been set up to explore the possibilities. Thus, it was predicted that an inhibitory analog of tocopherol would cause resorptive interruption of pregnancy in mice, and it was shown that α-tocopherol quinone would bring about such a result (127). By knowing the pharmacological manifestations of a deficiency of a metabolite, the effects of a metabolite analog may be in part anticipated. Again, certain hormones cause disease because they are either produced at an excessive rate or are destroyed abnormally slowly. It might be possible to neutralize the effects of the excess hormone by administration of an inhibitory analog. Such analogs of thyroxine have been formed, and shown to counteract toxic doses of the hormone given to tadpoles (128). Furthermore, abundant experimentation is being carried out to learn whether some of the agents antagonistic to histamine and effective against anaphylactic shock and against certain allergic reactions, may be viewed as competitive structural analogs of histamine (17).

The idea that various drugs act by combining with specific portions of the cell, and thus preventing the normal metabolites from reacting, goes back to the time

of Ehrlich. Since the evidence for this view, and the examples of it have been lucidly expounded by Clark (183), and recent developments especially in relation to participation of sulfhydryl compounds in these processes, by Roblin (17), no discussion will be included here.

Applications to Biochemistry. Inhibitory structural analogs of metabolites have appealed to many investigators as powerful tools with which to examine biochemical reactions. By specifically interfering with one process it may be possible to discover secrets of metabolism which have eluded us. As with all new tools, however, there must be a period of learning how to use them, and so with these there has been some fumbling. As a result much of the earlier work has been richer in speculation and hypothesis than in pertinent experimental observation. Let us scan the work along this line then more with the idea of seeing the type of use to which analogs have been and are being put, rather than with the hope of reviewing each individual contribution.

Several authors have concluded from their data on antagonisms that a given metabolite has a variety of functions. Now this view is not new, but in the case of some vitamins, it added to our knowledge. Thus, Shive and Roberts (186) have postulated several functions for p-aminobenzoic acid because of the existence and behaviour of several antagonists to sulfonamide drugs. Previously, Woolley (68) had considered the possibility of varied rôles for nicotinic acid, because of the way in which acetylpyridine affected animals and microorganisms.

Whatever may be the merits of these postulations there is no doubt that different types of inhibitory analogs of the same metabolite exert qualitatively different biological effects. Thus although thiopanic acid (pantoyl taurine) and phenyl pantothenone are two differing but close analogs of pantothenic acid, and both compete with the vitamin in the growth of bacteria, their qualitative effects are rather dissimilar as witnessed by the fact that thiopanic acid is ineffective in the treatment of malaria, or in the prevention of growth of non-pantothenic acid-requiring microorganisms while phenyl pantothenone possesses these powers. Or again, there are four types of structural analogs of vitamin K, represented by 3,3′-methylenebis-(4-hydroxycoumarin), iodinin (a phenazine oxide), α-tocopherol quinone, and 2,3-dichloronaphthoquinone. The action of each of these compounds may be reversed by vitamin K, but of them only the first influences the prothrombin level of plasma, and whereas the first causes generalized hemorrhages in animals, the third induces bleeding only from the reproductive tract, and that only in pregnant animals (127). The first is only weakly active in the inhibition of growth of bacteria, and in this process is not antagonized by vitamin K, while the fourth is highly potent against certain microorganisms in which its effect may by antagonized by vitamin K.

Obscure interrelationships between metabolites have been indicated by observations with their analogs. Here too as in the former cases, other types of evidence frequently pointed to similar conclusions. Thus, α-tocopherol quinone, an analog both of vitamin K and of tocopherol, called forth pharmacological signs similar to those seen in deficiency of the latter vitamin, but these manifestations were negated only by the former (127). Some metabolic relationship

between tocopherol and vitamin K seemed indicated. The experiments with sulfonamides led to the postulation of p-aminobenzoic acid as a metabolite (20) and this hypothesis was amply verified subsequently. The fact that tryptophane intake reduced the requirement for nicotinic acid, which has led to the postulation of tryptophane as the precursor of nicotinic acid (191), was discovered without the conscious use of analogs, but the interrelationship was exemplified again by the use of 3-acetylpyridine (187). Furthermore, the original demonstration may have depended on the existence of an analog of the vitamin in the corn used in the diet (192). Shive and Macow (12) have felt that the effects of pantothenic acid on the antagonism between aspartic acid and its hydroxy derivative indicated that aspartic acid was the precursor of the vitamin.

Because of the greater activity of cocarboxylase as compared to thiamine in antagonizing the microbiostatic effects of pyrithiamine, Sarett and Cheldelin (120) concluded that the vitamin was probably attached to the protein part of thiamine-containing enzymes before the pyrophosphate ester was formed. Similar findings with analogs of riboflavin led Sarett (109) to the same view with respect to the functioning of that vitamin, namely, that the metabolite was joined to the protein before phosphorylation converted the former into a coenzyme. However, these would not constitute unique explanations of the experimental data.

Several studies have been made of the use of inhibitory structural analogs of metabolites for the specific inhibition of various enzymes. Not only have new inhibitors of old enzymes been found, but also the existence of previously unrecognized enzymic reactions has been discovered. Sealock and Goodland (124) showed that the enzymic splitting of thiamine by carp thiaminase (193, 194) could be inhibited competitively by the thiamine analog o-aminobenzyl-methylthiazolium chloride, and that the oxidation of tyrosine by liver slices, a process catalyzed by ascorbic acid, was inhibited by glucoascorbic acid (15). Likewise von Euler and Ahlström (195) reported an interfering action of pyridine-3-sulfonic acid in the dehydrogenation of lactate by cozymase containing systems. The interpretation of these findings was made more complex by the fact that several unrelated compounds (e.g., salicylic acid) could replace pyridine-3-sulfonic acid. Perhaps some of the obscurity in interpretation of these results resided in the fact that the analog was being used to compete with a coenzyme rather than for a substrate. An investigation of the effects of nicotinic acid analogs on the enzymic synthesis of cozymase might provide more interpretable data. (Compare the discussion of mechanism above). Paget and Vittu (196) have reported that phospho-mono-esterase of erythrocytes is retarded in action by sulfanilamide and that this effect is reversed by p-aminobenzoic acid. In view of this finding a search for the function of the latter metabolite in the enzyme-system might prove profitable.

However, the mere inhibition of an enzymic reaction by a metabolite analog is not trustworthy evidence that the related metabolite is actually an integral part of the system. For example, although sulfanilamide interferes with the action of carbonic anhydrase (197), there are no data to indicate that p-amino-

benzoic acid is concerned with the enzymic process. The effect of the analog is not reversed by p-aminobenzoic acid, and furthermore, other sulfonamides which compete with the metabolite do not inhibit the action of the enzyme. In this instance sulfanilamide seems to possess a biological property not related to its competition with the structurally similar p-aminobenzoic acid. Many chemical compounds are harmful to enzymic reactions, so that it is understandable that metabolite analogs may have effects other than those related to their competitive behaviour.

A new enzymic process, namely, that of the conversion of pantothenic acid into a conjugated form in streptococcal cells was discovered by McIlwain through the use of the analog thiopanic acid (83). This reaction of the vitamin was intimately coupled with glycolysis but by judicious use of inhibitors, the pantothenic acid conjugating system could be differentiated from the glucolytic one. In similar fashion, Woolley (118) recognized a pyrithiamine-splitting system in certain microorganisms, the occurrence of which was correlated with the ability to synthesize thiamine.

The observation that a pair of structurally similar metabolites, which both occur in the same individual, may be competitively antagonistic to each other has led to the hypothesis that certain metabolic functions are regulated through the intermediation of this antagonism. For example, Granick and Gilder (101) considered that metabolism of porphyrins was in part regulated by the competition between protoporphyrin and copro-porphyrin. These two biologically important compounds were known to exist in the same individual, and yet in the growth of *Hemophilus influenzae* they were competitors. A similar view for the estrogens and androgens was mentioned briefly above (115). Possibly the antagonisms between analogous amino acids, such as that between glycine and alanine (7) may be viewed from this angle.

Compounds have been discovered in some species which are harmful to other living things, and which can be rendered harmless by an excess of structurally analogous metabolites. In other words, inhibitory structural analogs of metabolites are formed by one type of organism and act against other types. Thus, iodinin, a hydroxy phenazine oxide, is an antibiotic pigment formed by *Chromobacterium iodinum*. It competes with the structurally related vitamin K in the prevention of growth of streptococci (149). Again, a substance has been found in corn (maize) which is able to cause signs of pellagra in mice (192). The action of the compound was reversed either by nicotinic acid or by tryptophane. Because of these facts, and because of the chemical properties of the active substance, it was postulated that the agent might be an analog of nicotinic acid.[1]

[1] Since this paper was prepared the pellagragenic agent has been identified as indole-acetic acid (200). This compound may be viewed as derived from nicotinic acid by conjugation with a benzene ring and extrusion of a carbon atom from the pyridine ring. It is likewise an even better analog of tryptophane. Just as in the case of α-tocopherol quinone, which is related to both vitamin E and vitamin K, indole-acetic acid is at the same time an analog of two metabolites. In the latter instance either metabolite will reverse the effects of the analog.

This last example lacks force because the nature of the agent is still conjectural, but a better defined case of production of disease by a metabolite analog exists. *Fusarium lycopersici*, the cause of a common disease of tomatoes, produces a toxic substance which will reproduce the signs of the disease in plants. This agent has been isolated in pure form (198) and shown to be a tripeptide isomeric with serylglycylaspartic acid (199). The tomato-wilting powers of this peptide are negated by the related serylglycylglutamic acid, or glutathione, or by strepogenin, and these latter peptides have been shown to function as required nutrients for several species of bacteria (199). The Fusarium probably is able to cause disease by forming an inhibitory structural analog of a metabolite. The logical step would be to treat the infection with the metabolite. The elucidation of the structure of the antagonist in this case was the key for solving the probable nature of the unknown metabolite, strepogenin.

Some Relationships of Structure to Antagonistic Activity. Generalizations have been made about the types of structural alteration which will convert metabolites into antagonistic agents (189). Despite some adverse criticisms (e.g. 18), and in the face of acknowledged shortcomings and limitations (189, 159) the ideas contained in these generalizations have continued to lead to the production of new metabolite-inhibitors. The basis for these rules may be seen from table 2. This is that alteration of the structure of a metabolite in certain defined ways results in the formation of agents which compete with it. Some of these types of alteration are: the replacement of a carboxyl group with a sulfonic acid or sulfonamide radical, or by a ketone; the substitution of one atom for another in the ring system of the metabolite; and the replacement of alkyl side chains of aromatic ring systems with halogens. These are only a beginning in the classification of generalizations about the relationships of chemical constitution to antagonistic activity, because many examples could be cited of other types of alterations in structure which lead to inhibitory analogs (3). Furthermore, Woolley (189) has pointed out that there is no single way in which the structure of a vitamin or hormone must be altered in order to obtain a competitor to it. As we saw in the previous section, there may be pronounced qualitative differences in effects produced by different types of analogs of the same metabolite. As knowledge about the phenomenon of antagonism between structurally similar compounds accumulates it is probable that these postulations will be both modified and expanded.

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